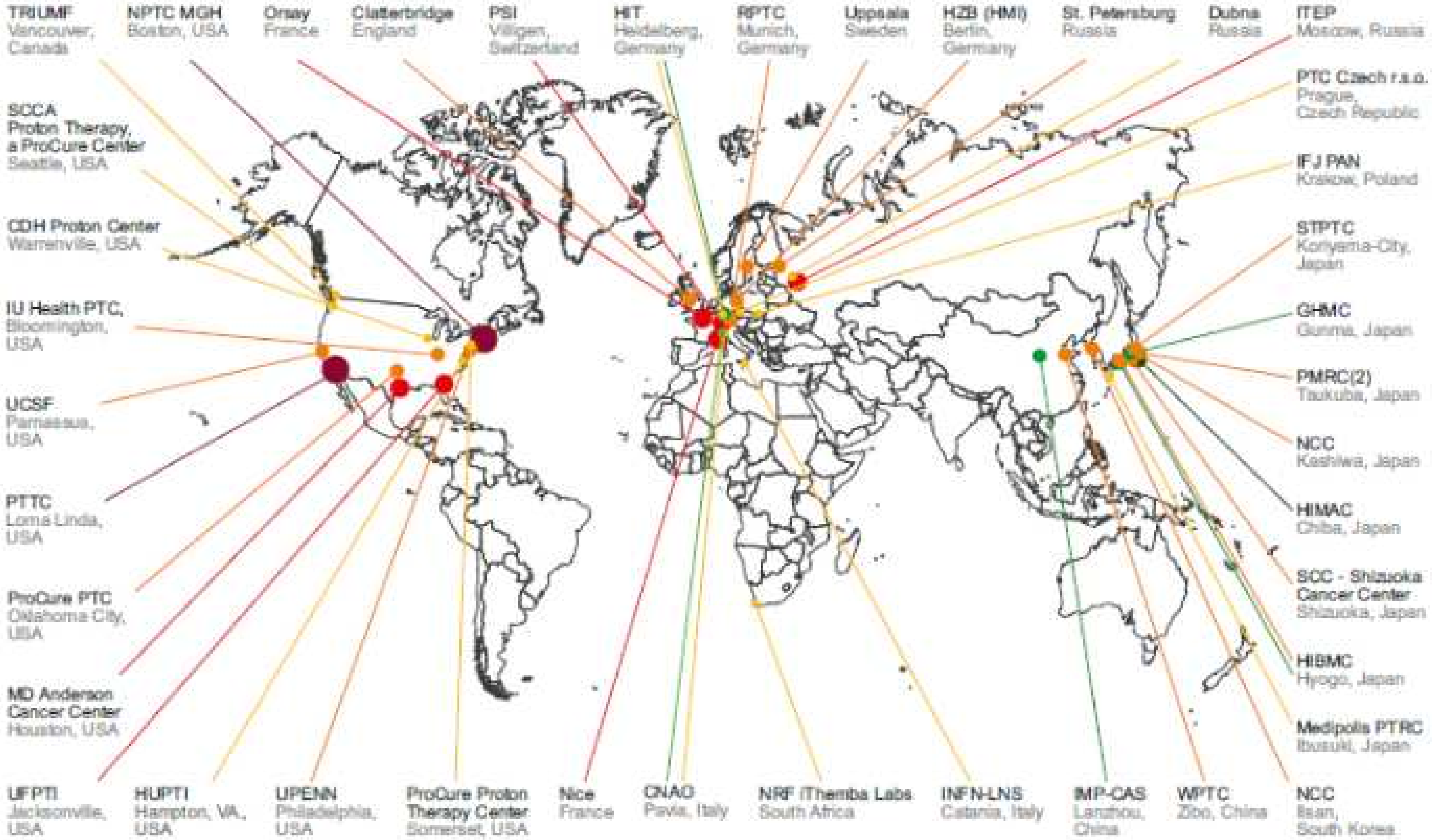
February 13, 2018 Cogne

Heavy ions in therapy and space – part I

Particle therapy

Marco Durante

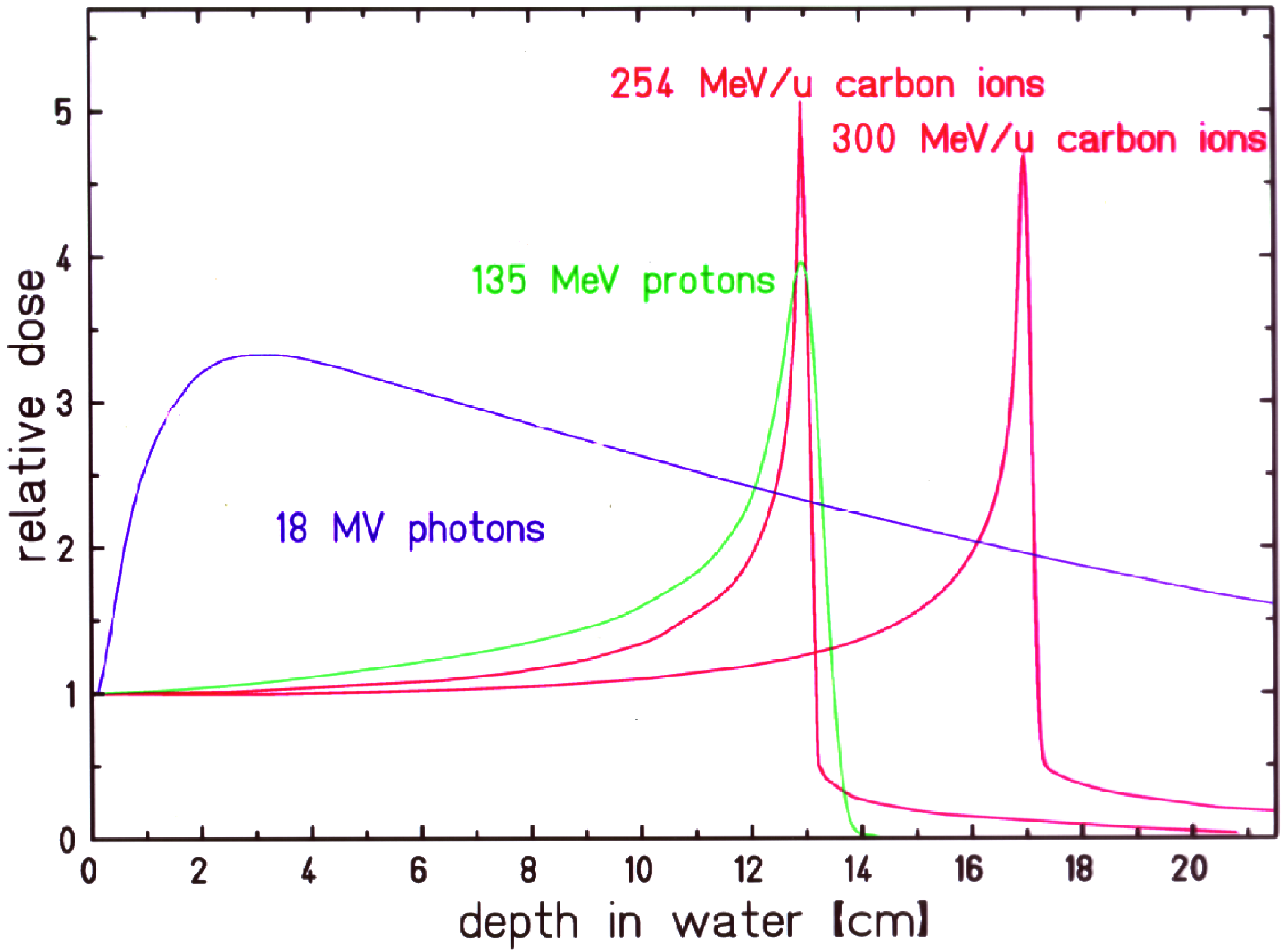


- **March 2014: 44 proton/7 heavy ion centers**
- **Under construction: 25 proton/ 4 heavy ion centers**
- **Only in USA, 27 new centers expected by 2017**

Nuclear Physics European Collaboration Committee (NuPECC)

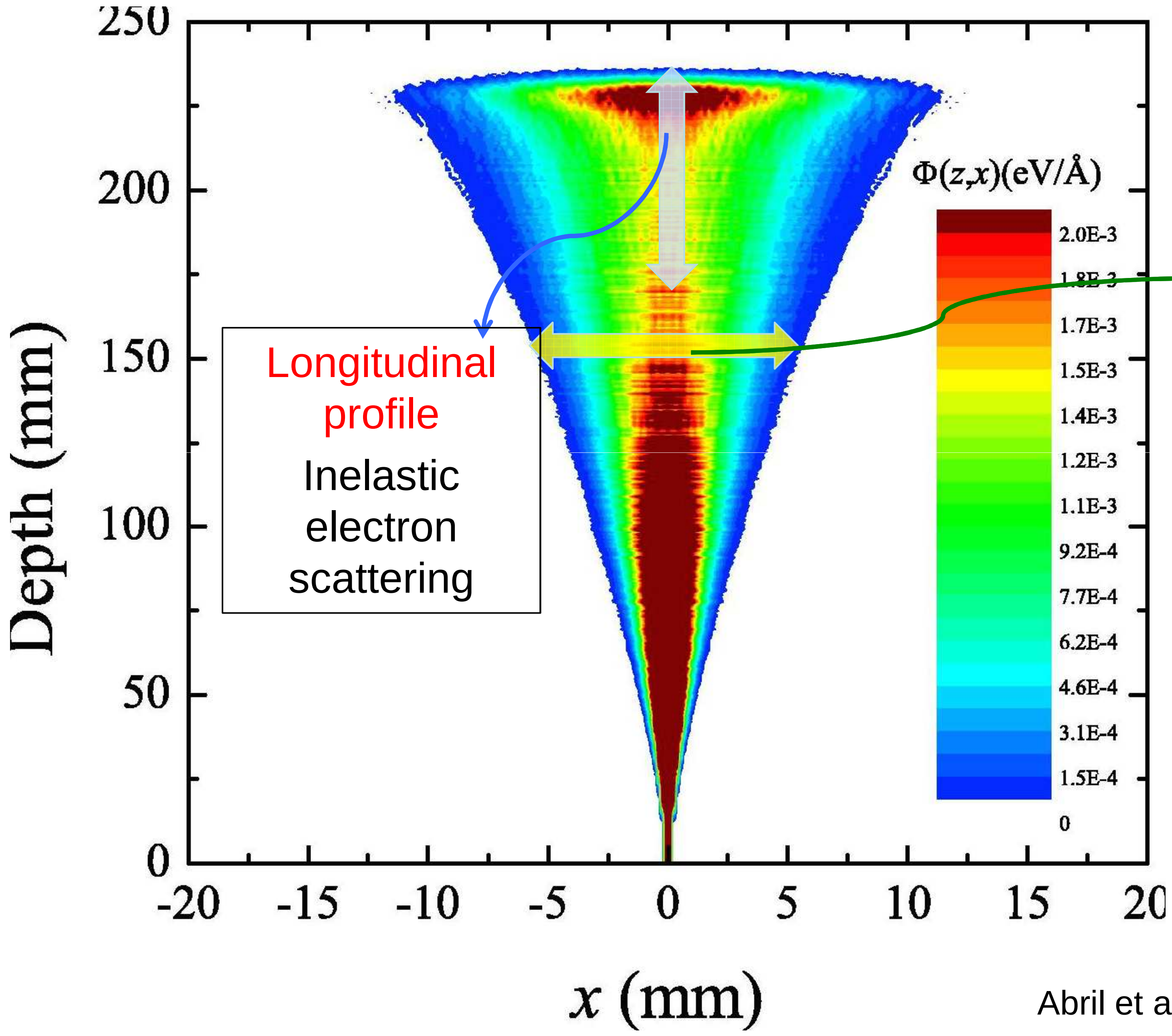
Nuclear Physics for Medicine

•Depth dose distribution of various radiation qualities



Charged particle therapy physics

Universitat d'Alacant
Universidad de Alicante
Departament de Física Aplicada
Departamento de Física Aplicada

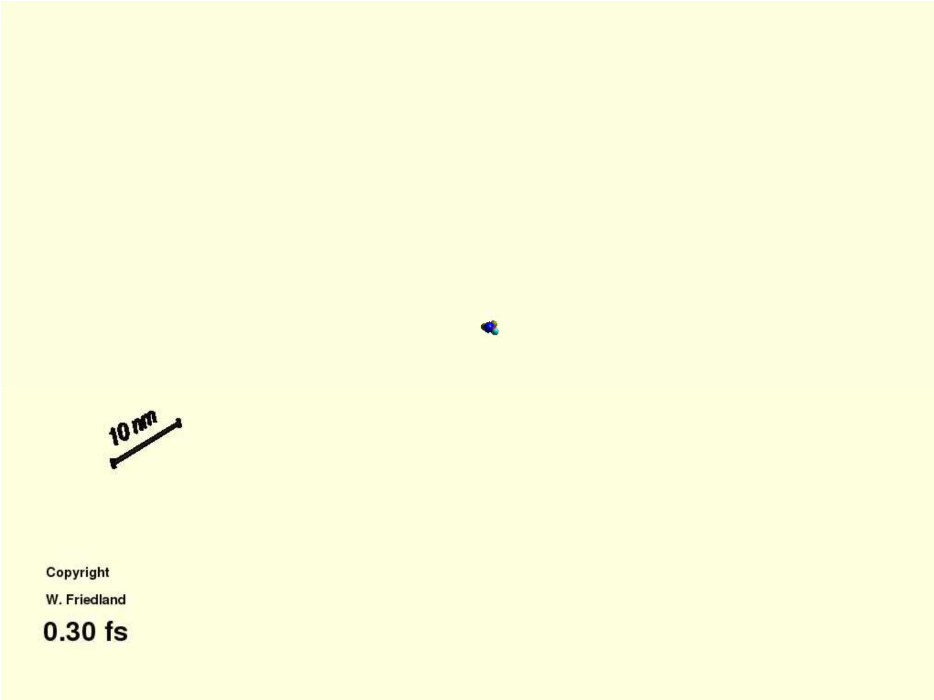


200 MeV protons in water

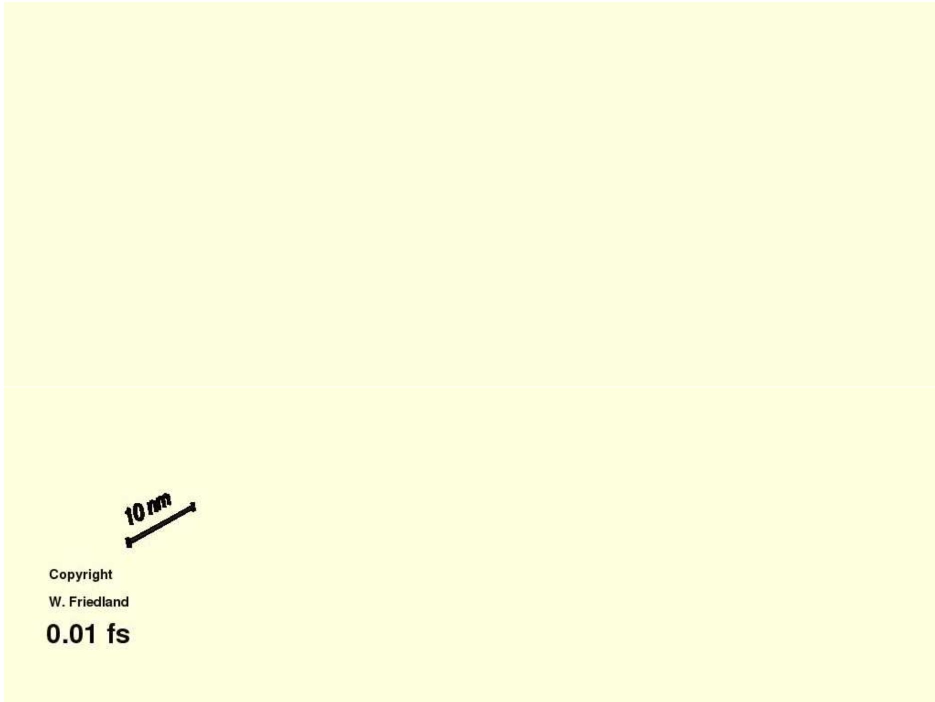
Abril et al., NIMB 2015

Light vs. heavy ions at the same linear energy transfer (LET=140 keV/μm)

α-particles, 2 MeV



Fe-ions, 1 GeV/n

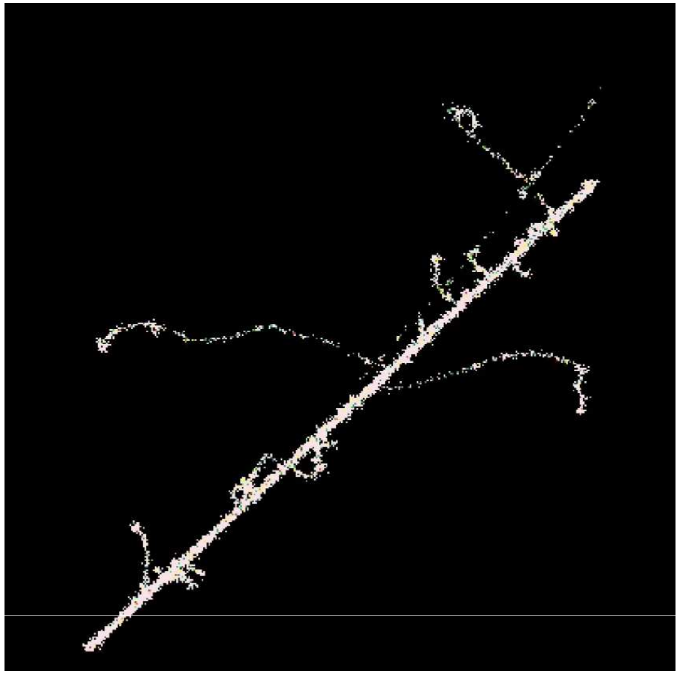


courtesy of Werner Friedland

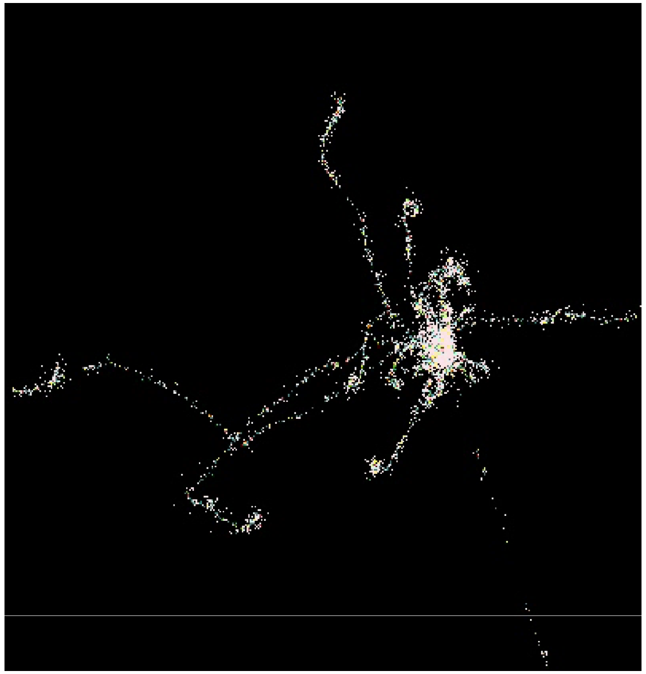
HelmholtzZentrum münchen
Deutsches Forschungszentrum für Gesundheit und Umwelt

Track structure: from physics to chemistry....

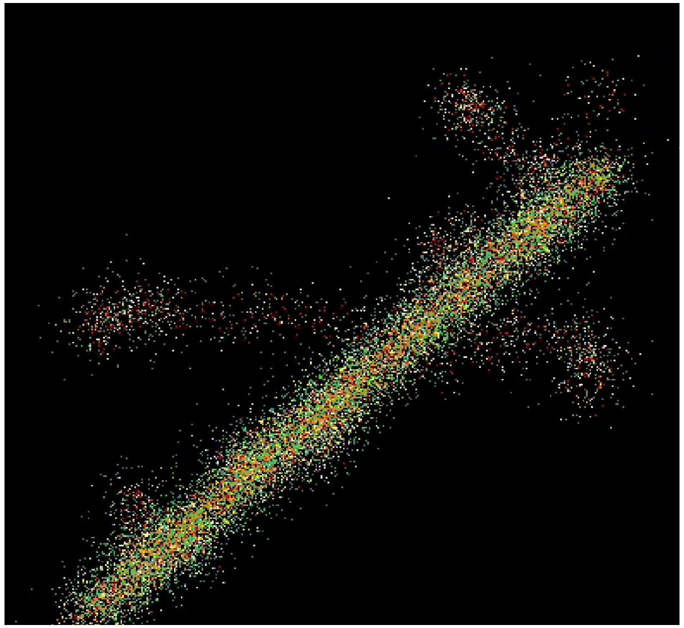
courtesy of Iannick Plante, USRA

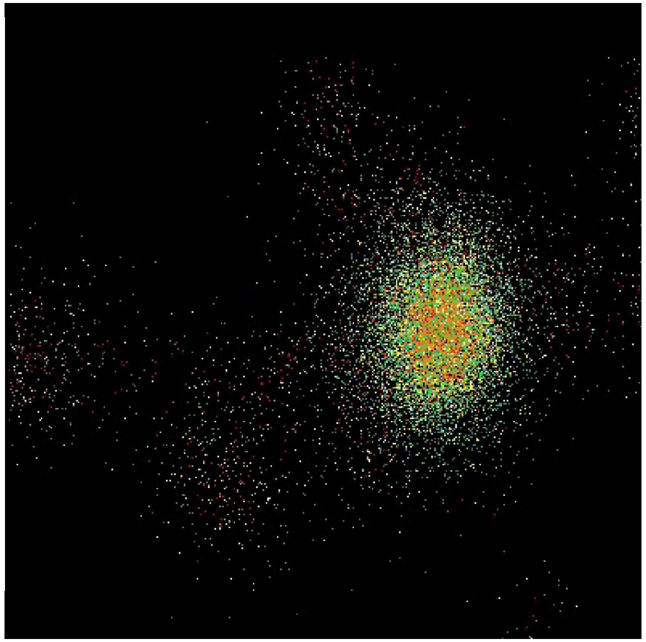


300 MeV/n C-ions in water



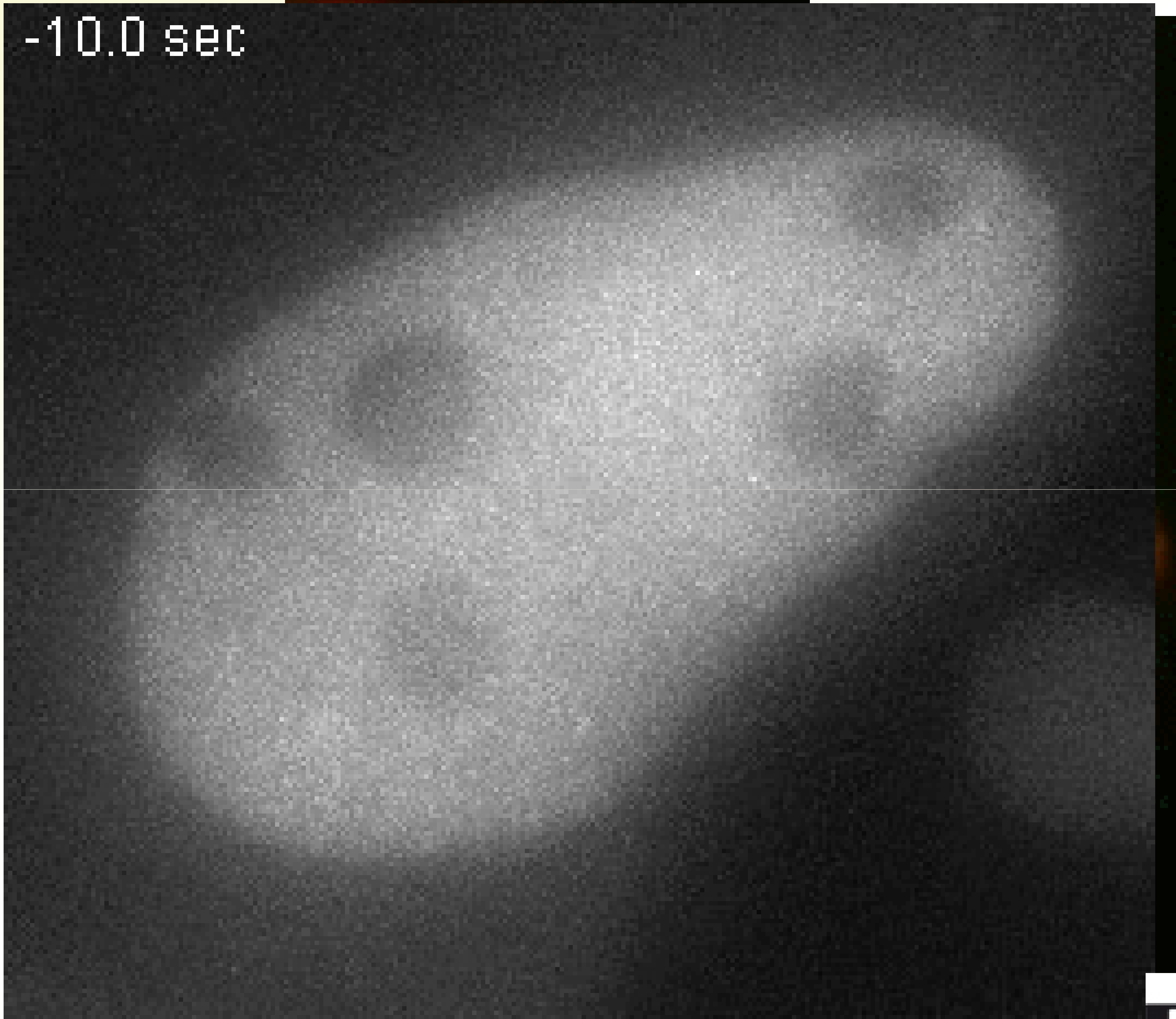
10^{-12} s





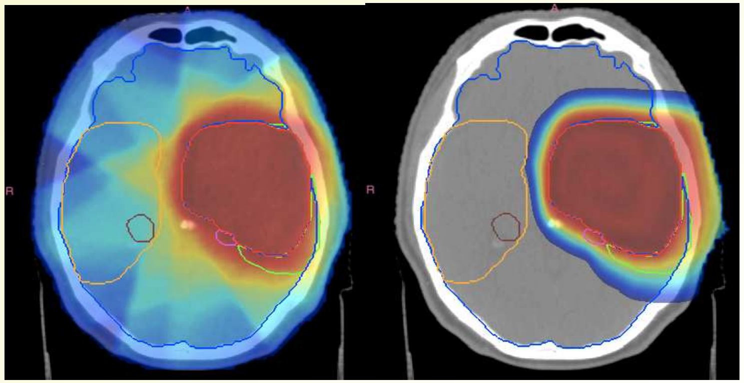
10^{-6} s

•Live cell imaging of heavy ion traversals in euchrom

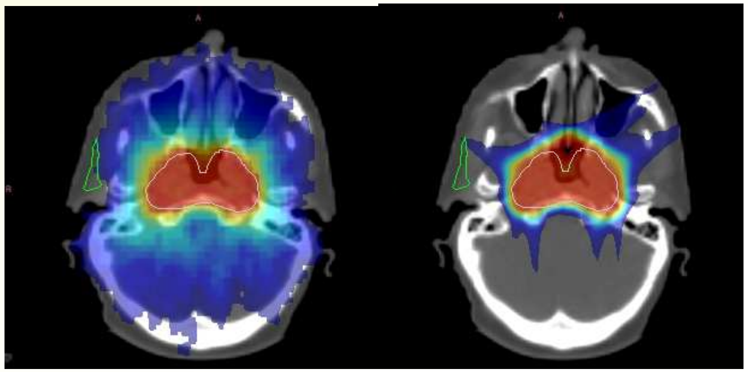


Sci. USA 2009; Nucl. Acids Res. 2011

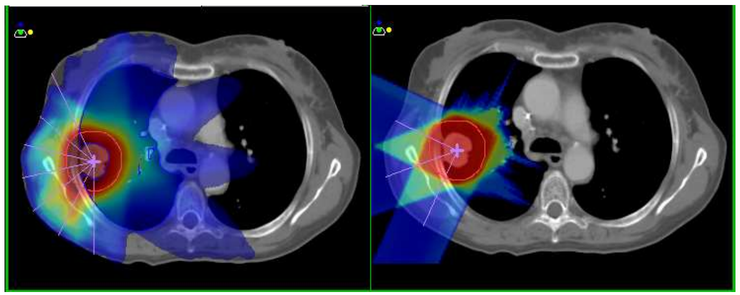
Sparing the normal tissue



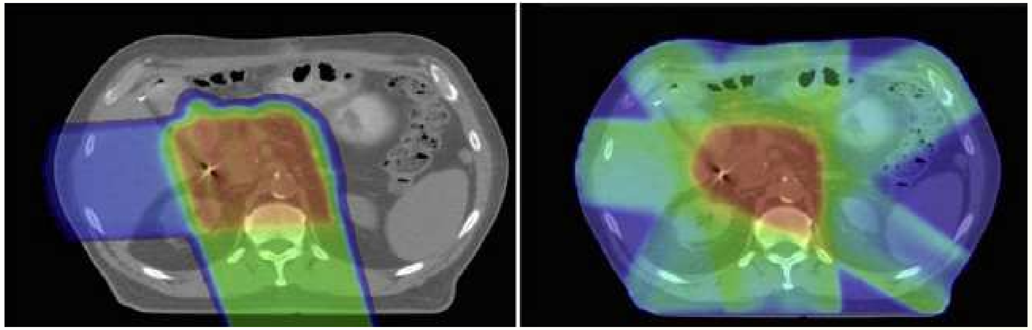
CNS



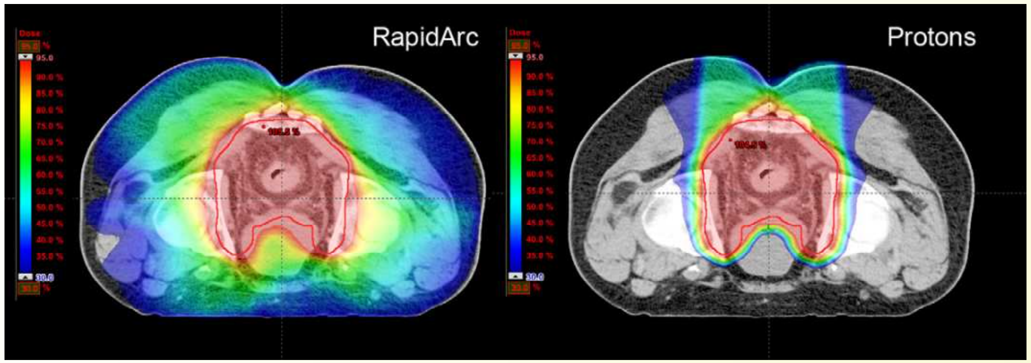
H&N



LUNG



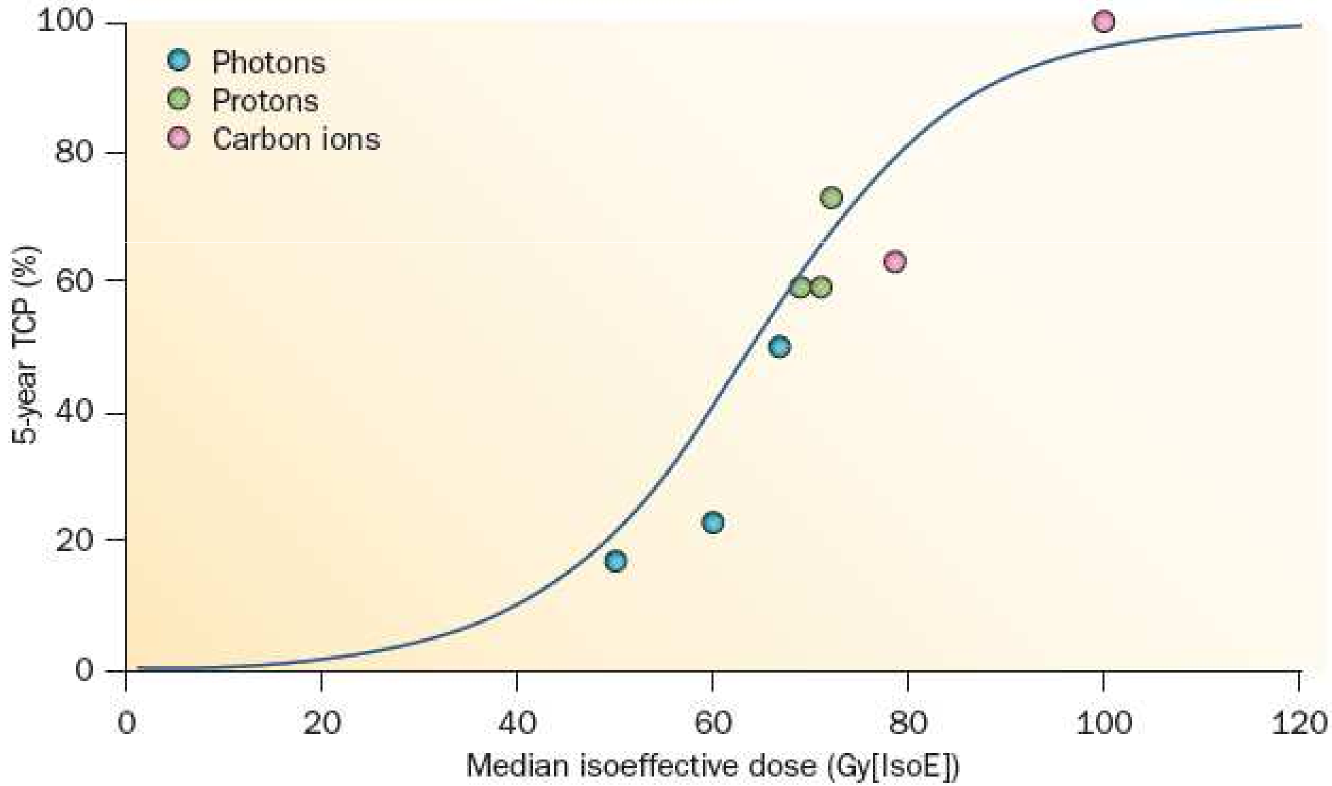
ABDOMEN



PELVIS

Courtesy of Marco Schwarz, TIFPA, Trento

Skull-base chordoma



Loeffler & Durante, *Nat. Rev. Clin. Oncol*. 2013

Nuclear physics: new solutions to set the controversy

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

BMJ VOLUME 327 20–27 DECEMBER 2003

Gordon C S Smith, Jill P Pell

BMJ
British Medical Journal

Proton Therapy for Prostate Cancer

Although this is the most common use of proton therapy, controversy remains

BJC
British Journal of Cancer (2013) 108, 1225–1230 | doi: 10.1038/bjc.2013

Keywords: proton beam; radiation; prostate cancer; quality of life; cost; evidence

Proton beam therapy and localised prostate cancer: current status and controversies

J A Efstathiou*,[1], P J Gray[1] and A L Zietman[1]

[1]Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

Particle therapy "perceived as too expensive, too complicated, not enough precise and reliable" (from *Bloomberg Business*, 2012)

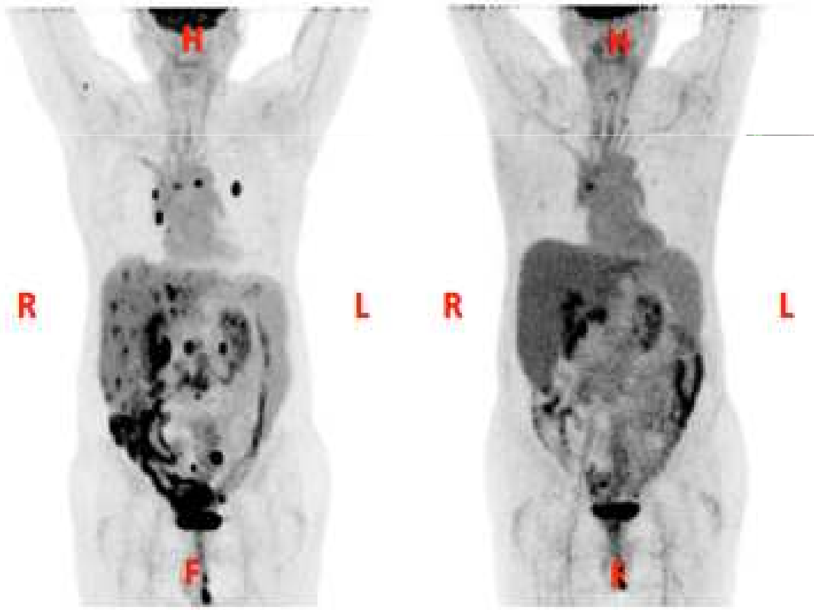
Table 1 | Ongoing randomized clinical trials comparing different radiation modalities for the same disease

Study	Institution	Phase	Condition	Radiation arm 1	Radiation arm 2
R03CA188162: IMPT vs IMRT	MDACC	III	Oropharyngeal cancer (head and neck cancer)	Protons*	X-rays*
PARTIQoL (NCT01617161): proton therapy vs IMRT	MGH	III	Low-risk or intermediate-risk prostate cancer	Protons	X-rays
NCT01512589: proton-beam therapy vs IMRT	MDACC	III	Oesophageal cancer	Protons*	X-rays*
RADCOMP (NCT02603341): pragmatic randomized trial of proton vs photon therapy	PTCORI	III	Post-mastectomy stage II or III breast cancer	Protons	X-rays
NRG BN001: dose-escalated IMRT or IMPT vs conventional photon radiation	NRG Oncology	II	Newly diagnosed glioblastoma	Protons*	X-rays*
NRG 1542: proton radiation vs conventional photon radiation‡	NRG Oncology	III	Hepatocellular carcinoma	Protons	X-rays
NCT01182753: proton radiation vs carbon-ion radiation therapy	Heidelberg University, Germany	III	Low-grade and intermediate-grade chondrosarcoma of the skull base	Protons	Carbon ions
NCT01182779: proton radiation vs carbon-ion radiation therapy	Heidelberg University, Germany	III	Chordoma of the skull base	Protons	Carbon ions
CLEOPATRA (NCT01165671): proton radiation vs carbon-ion radiotherapy	Heidelberg University, Germany	II	Primary gioblastoma	Protons*§	Carbon ions*§
IPI (NCT01641185): proton radiation vs carbon-ion radiotherapy	Heidelberg University, Germany	II	Prostate cancer	Protons	Carbon ions
ISAC (NCT01811394): proton radiation vs carbon-ion radiation therapy	Heidelberg University, Germany	II	Sacrococcygeal chordoma	Protons	Carbon ions
ETOILE (NCT02838602): carbon-ion radiotherapy vs IMRT	Lyon University Hospital, France	III	Radioresistant adenoid cystic carcinoma and sarcomas	Carbon ions	IMRT
BAA-N01CM51007-51: prospective trial of carbon-ion therapy vs IMRT	NCI	I/III	Locally advanced pancreatic cancer	Carbon ions*	X-rays*
CIPHER: prospective multicentre randomized trial of carbon-ion radiotherapy vs conventional radiotherapy	UTSW	III	Locally advanced pancreatic cancer	Carbon ions*	X-rays*

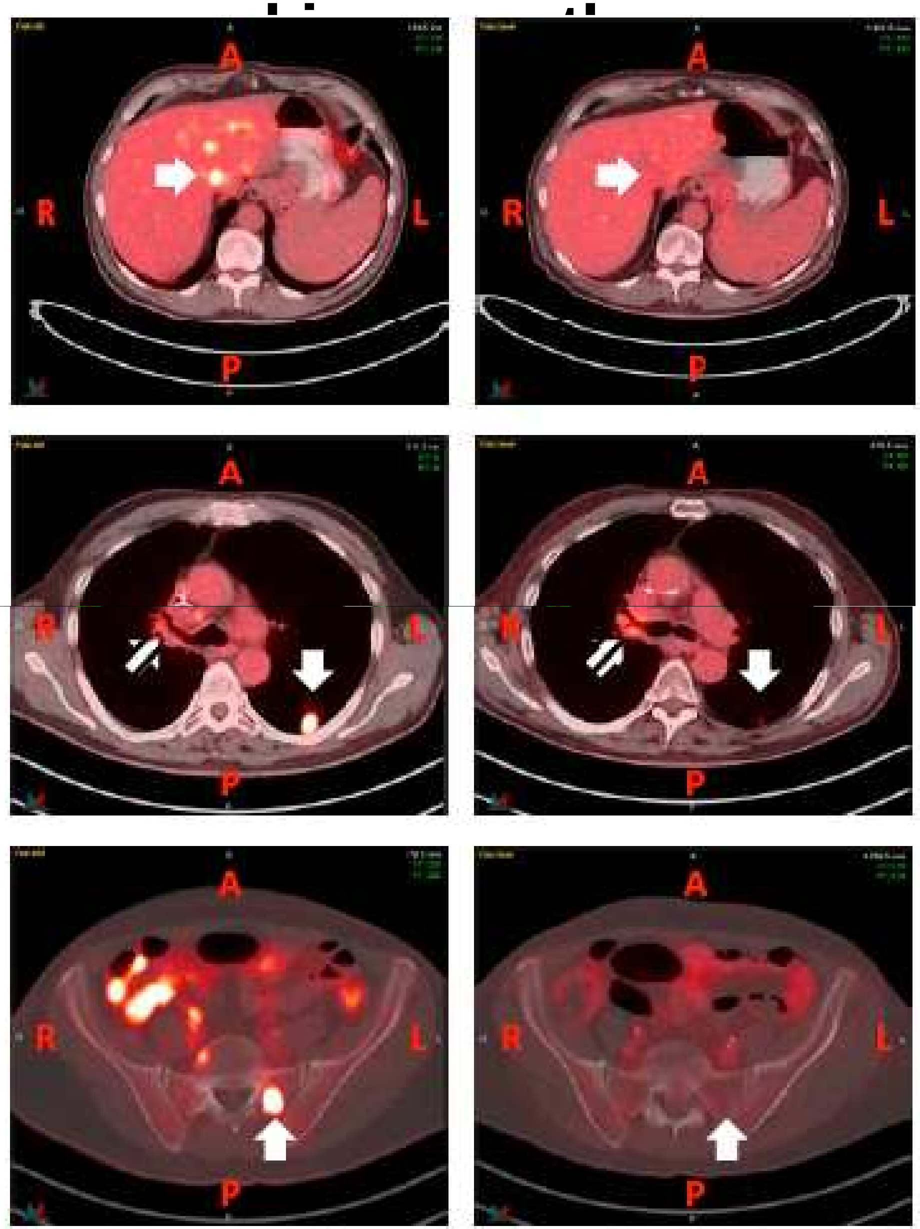
Durante *et al.*, *Nat. Rev. Clin. Oncol.* 2017

Combined radioth
in
lung

•NSCLC progressing after 3 lines of



August 2012 PET/CT January 2013 PET/CT

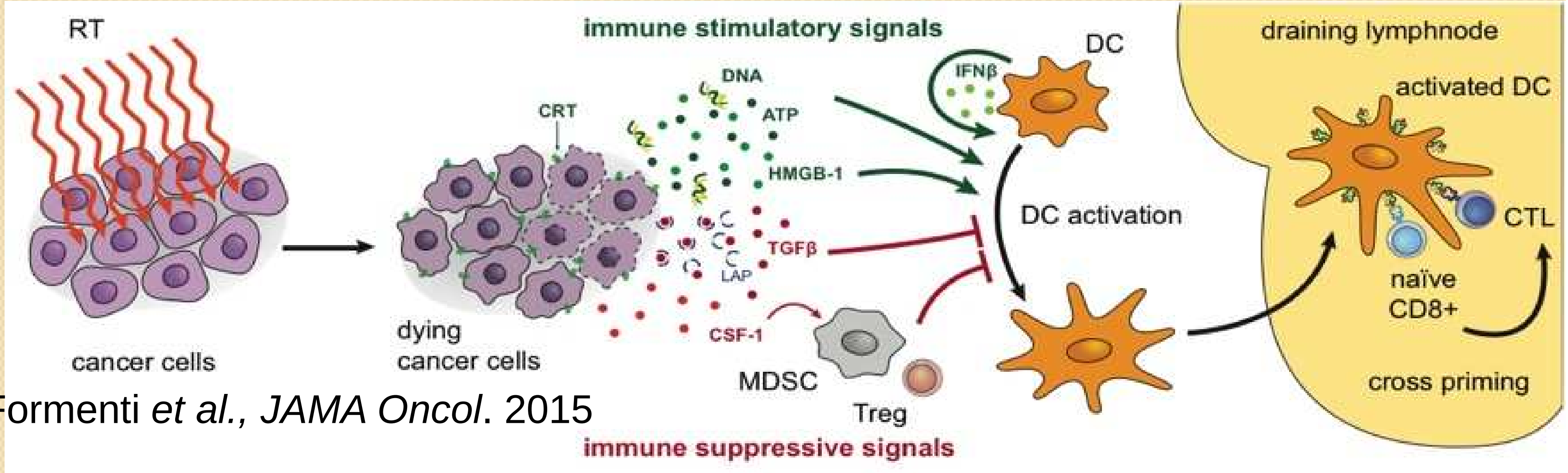


August 2012 PET/CT January 2013 PET/CT

•RT to one liver met 6 Gy X 5 (TD 30 GY)

•Ipilimumab, 3 mg/Kg, after first RT q3 weeks, X 4

RADIOIMMUNOTHERAPY



Formenti *et al.*, *JAMA Oncol*. 2015

Does Heavy Ion Therapy Work Through the Immune System?

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**Trento Institute for Fundamental Physics and Applications-National Institute for Nuclear Physics, University of Trento, Trento, Italy; †Center for Radiological Research, Columbia University Medical Center, New York, New York; and ‡Department of Radiation Oncology, Weill Cornell Medical College, New York, New York*

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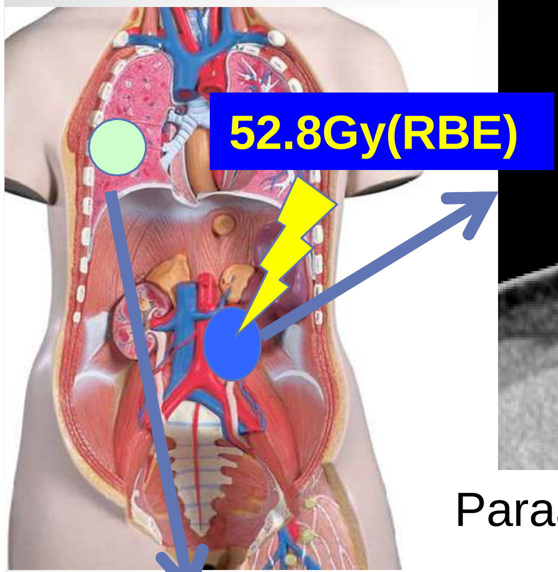
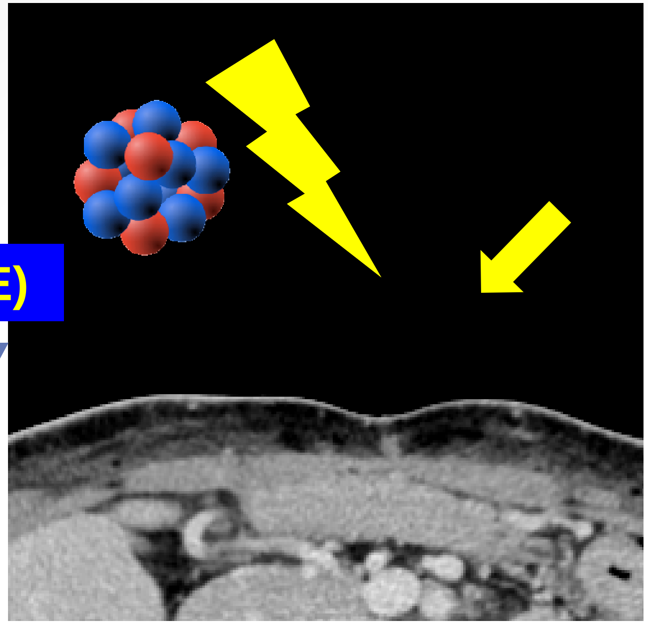
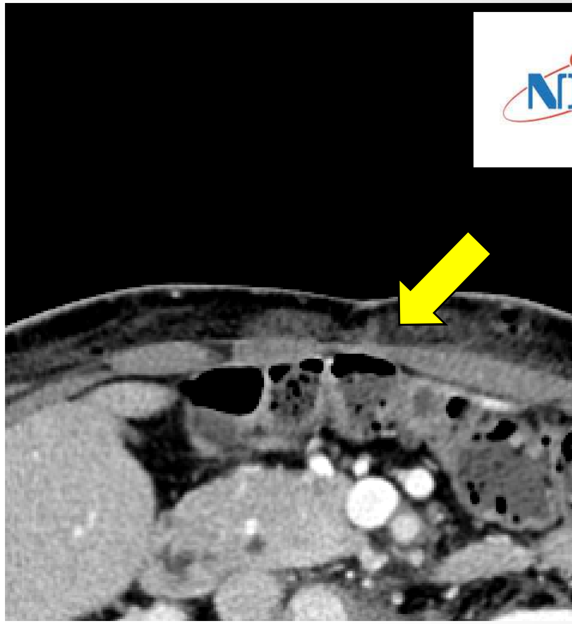
53 year old male pancreatic cancer recurrence after surgery

nivolumab180mg/
2weeks

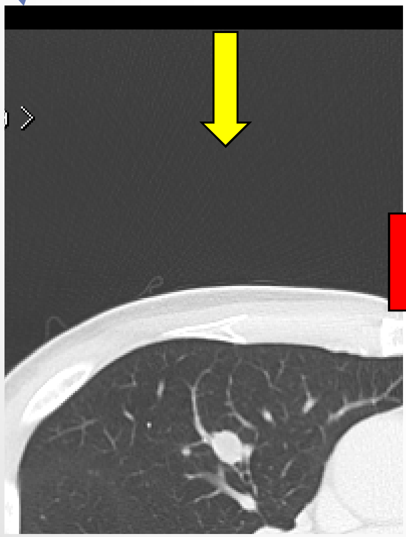




Paraaortic lymph node metastasis



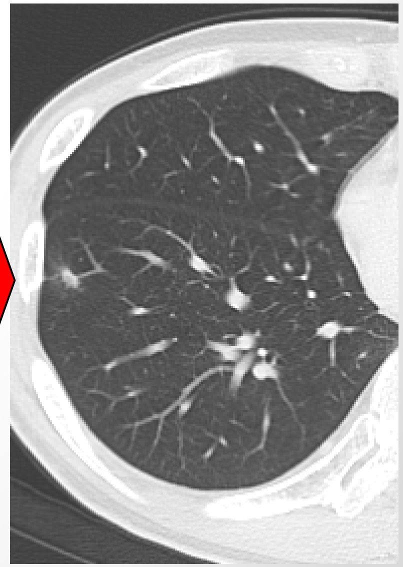
6 months after C-ions



Lung metastasis

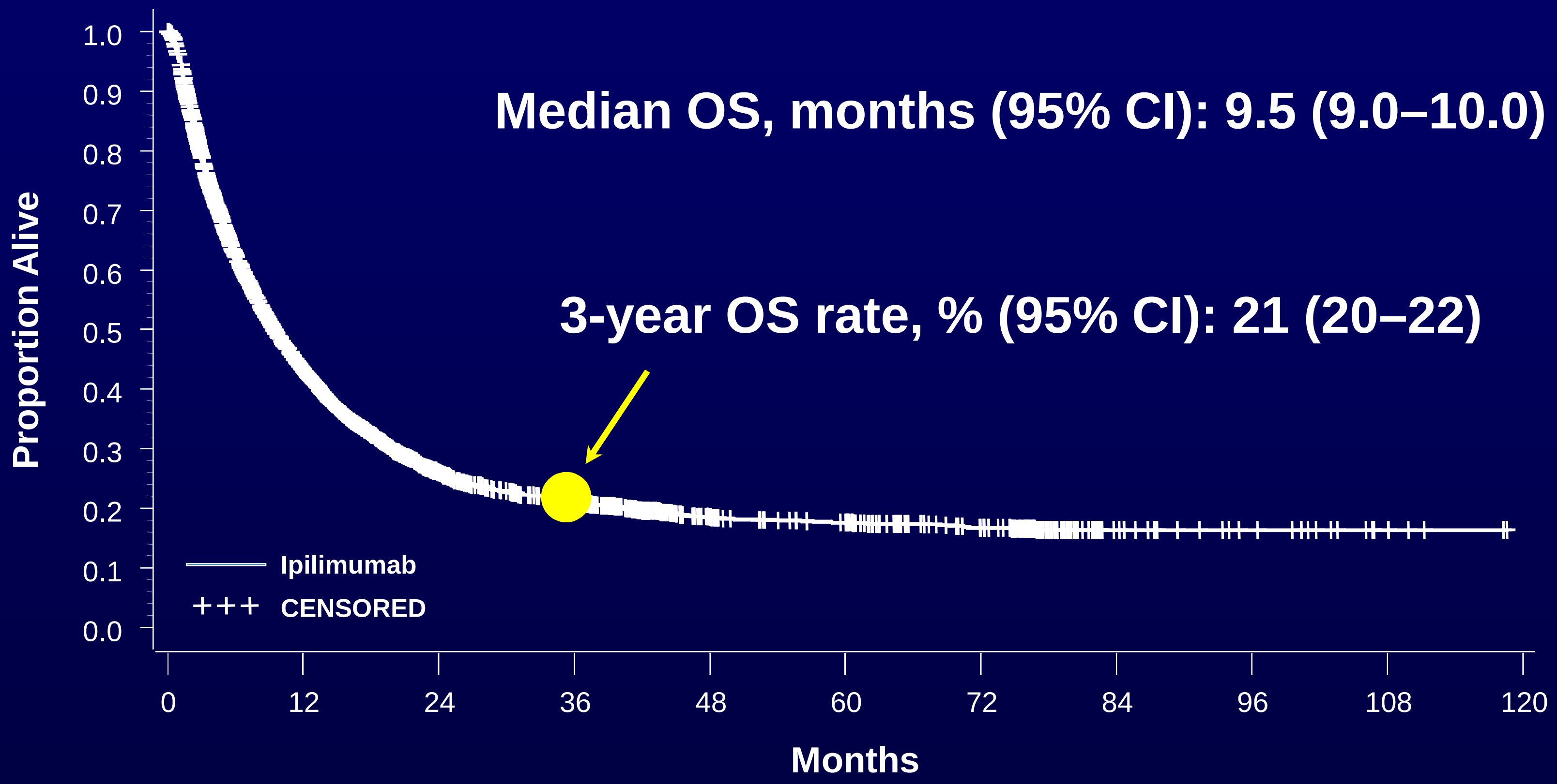
6 months after C-ions

Lung metastasis



6 months after C-ions

Does it work in all patients?



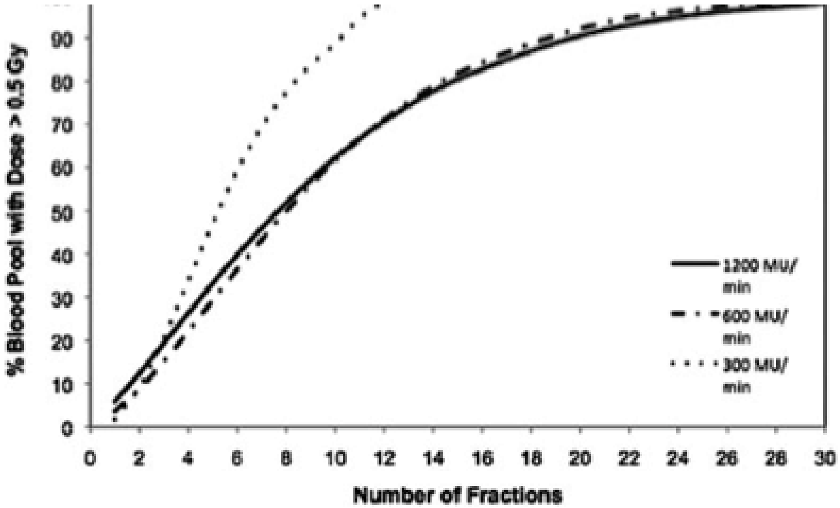
Ipilimumab in melanoma patiens – pooled OS analysis
In 4,846 patients

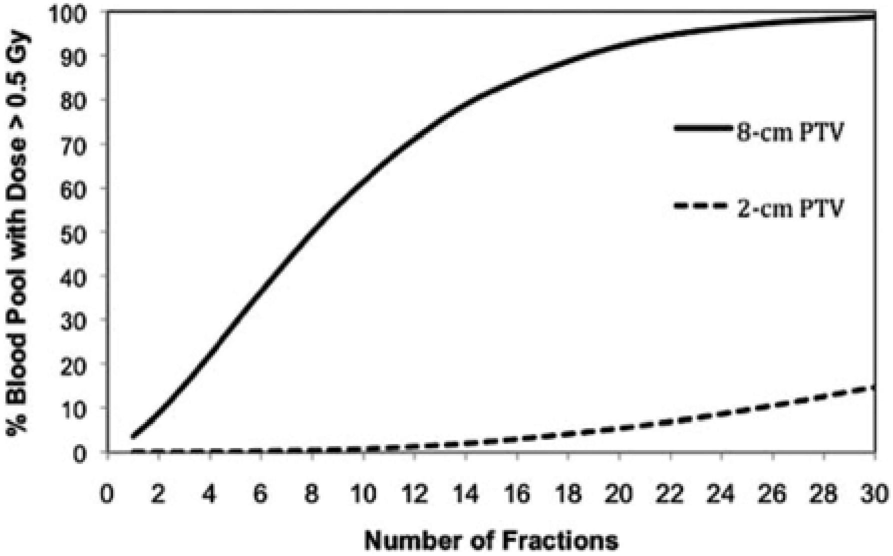
Schadendorf et al. JCO 2015

Statement: „we know everything about charged particle *physics*, but not about *biology*“

Answer: maybe, but to understand the *biology*, we have to start from the *physics*

Radiotherapy (and chemotherapy) compromise the immune system





A single radiation fraction delivered 0.5 Gy to 5% of circulating cells, after 30 fractions 99% of circulating blood had received ≥0.5 Gy

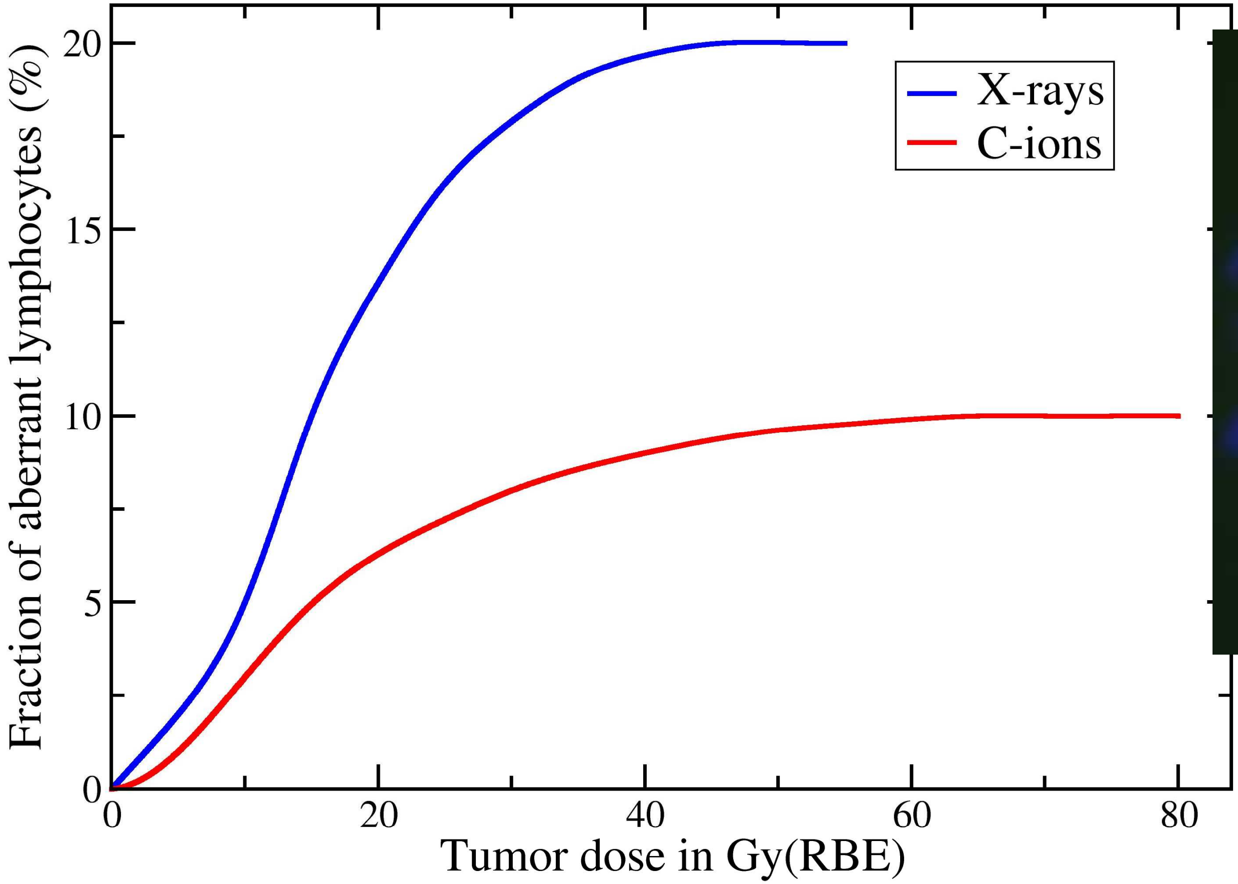
Circulating lymphocytes : D10 = 3 Gy
D50 = ~2 Gy
D90 = ~.5 Gy

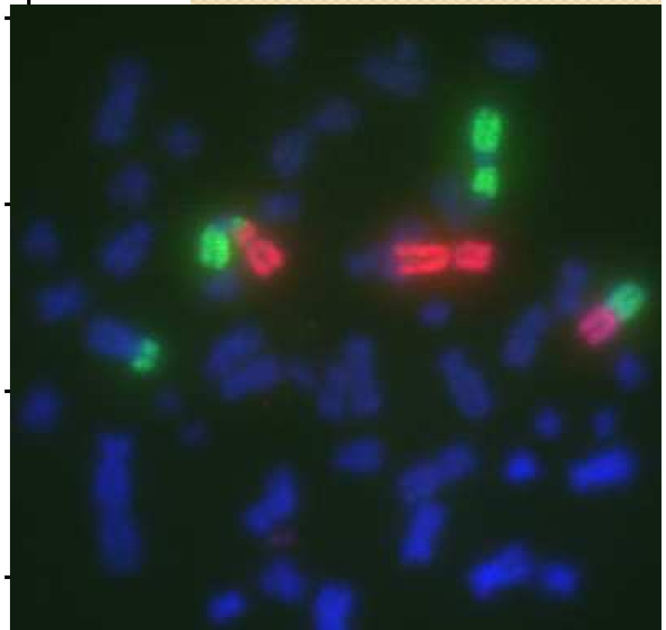
Need:

- High dose-rate
- Hypofractionation
- Reduced integral dose

Yovino *et al Cancer Invest.* 2013

Physical advantages of particle therapy for immunology



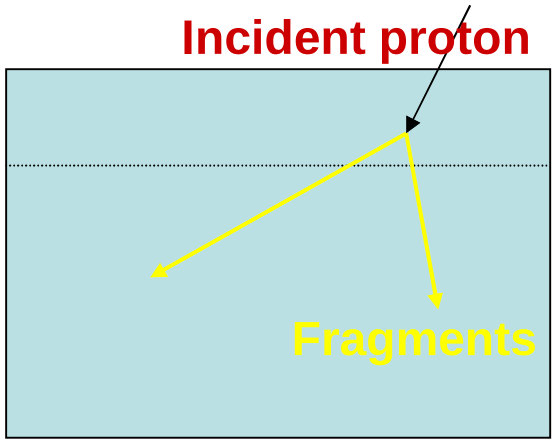


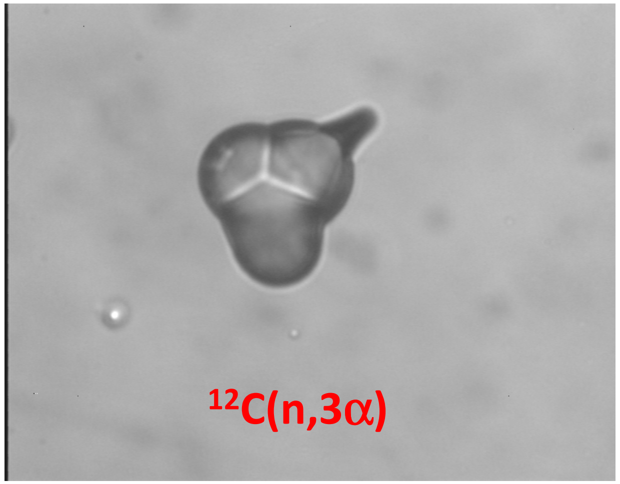
Durante *et al. Nat. Rev. Clin. Oncol*. 2017

Nuclear fragmentation in particle therapy

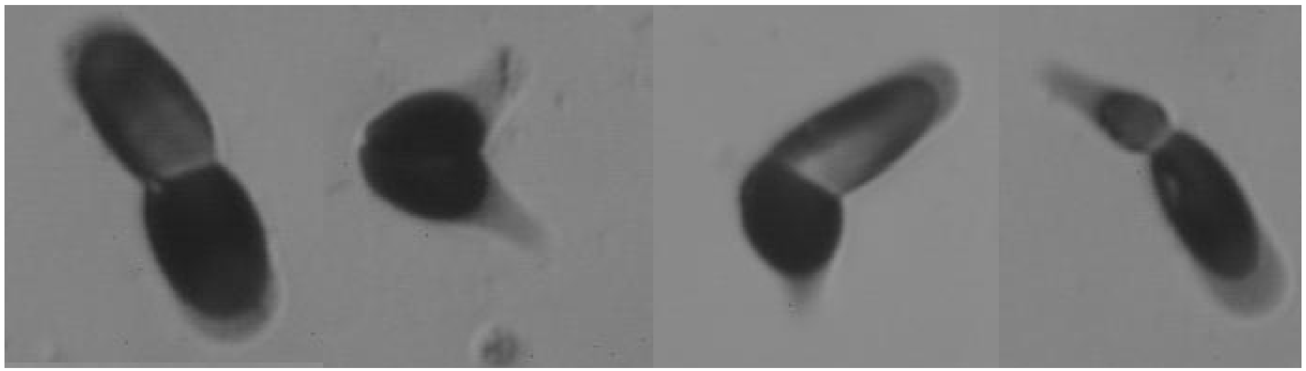
1. Target fragmentation: *breaking bad*
2. Projectile fragmentation: *wag the tail*
3. New ions: *wag the dog*
4. Range verification: *chase the fragment*

1. Target fragmentation





CR39 plastic track detector



The difference of mass number of products is visible.

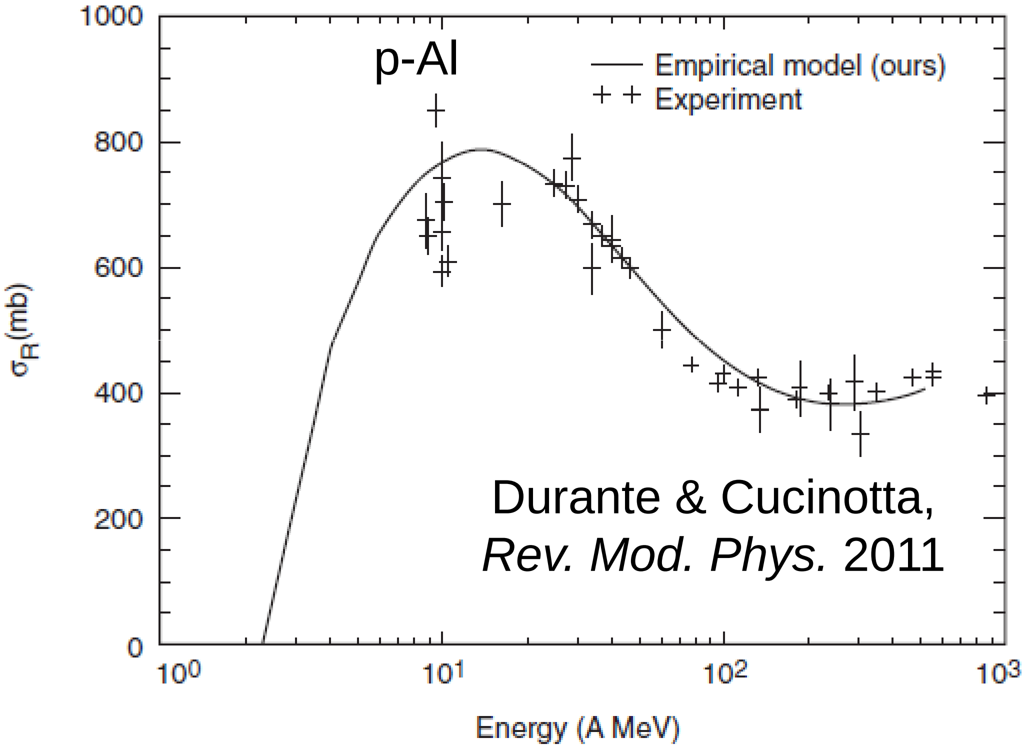
courtesy of J.K. Palfalvi, Budapest

- about 1% cm^{-1} H_2O of the protons undergo nuclear interactions
- about 20% in a typical treatment plan
- 60% of the energy is deposited locally by charged fragments
- 40% in *n* and γ out of the field
- unstable recoil nuclei: radiation safety, range verification by PET

Models of target fragmentation by protons

Fragmentation of ^{16}O	
^{15}O	$\sigma = 42mb$
^{15}N	$\sigma = 23mb$
^{14}N	$\sigma = 31mb$
^{13}C	$\sigma = 28mb$
^{12}C	$\sigma = 36mb$

$$\sigma_{\mathrm{ABS}} = \pi r_0^2 c_1(E)[A_p^{1/3} + A_T^{1/3} - c_2(E)]^2,$$



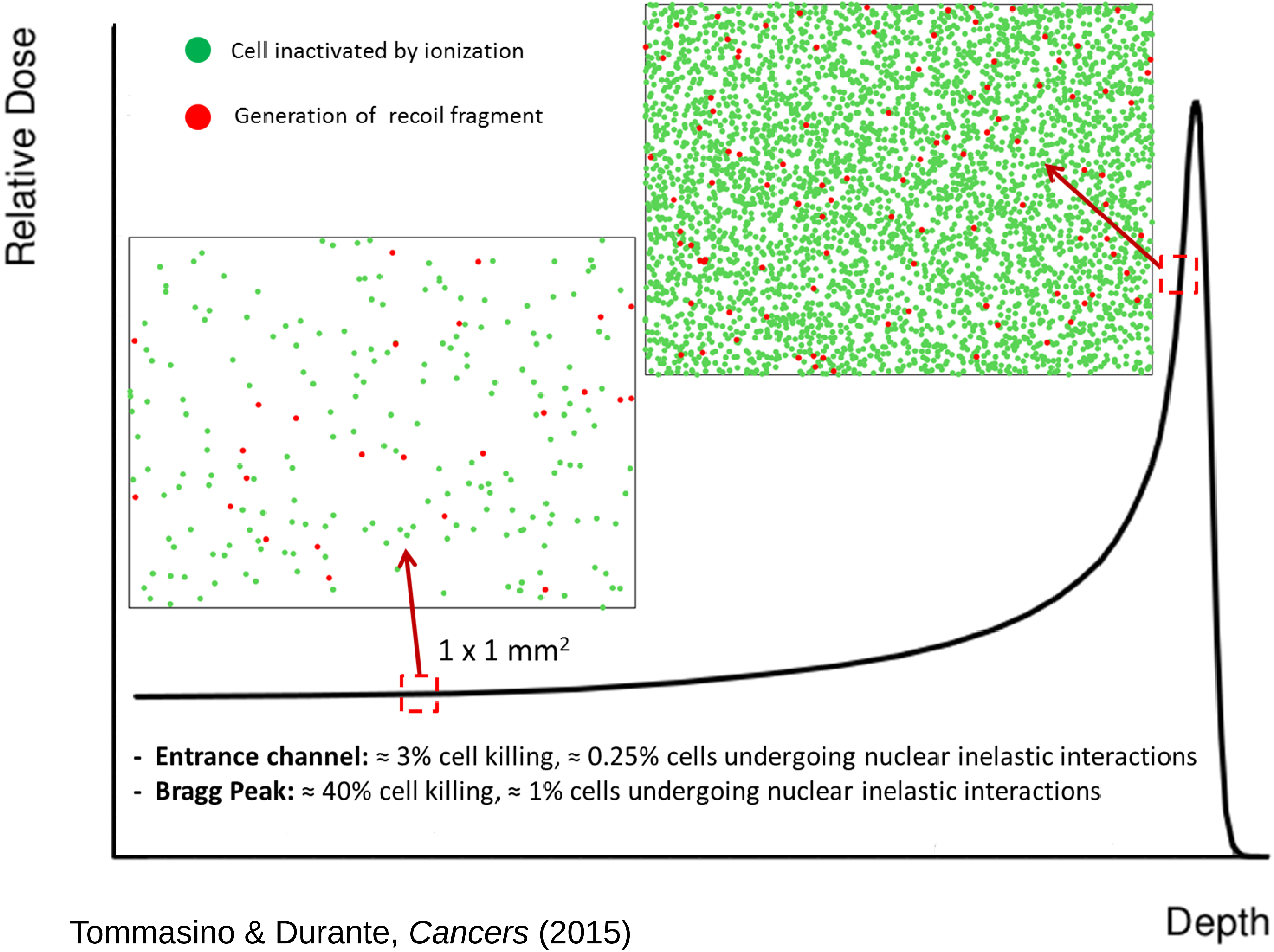
Fragmentation of ^{12}C	
^{11}C	$\sigma = 55mb$
^{11}B	$\sigma = 30mb$

Goldhaber formula

$$E_F \simeq 14,9 \left[\frac{A-F}{A-1}\right] \quad \text{MeV}$$

$$\sigma(p,N)_{\mathrm{reac}} = \pi r_0^2[1 + A_t^{1/3} - b_0(1 + A_t^{-1/3})]^2$$

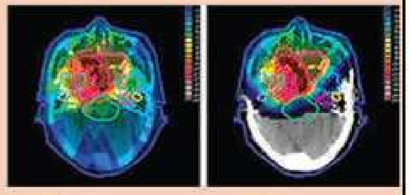
High-energy **Bradt-Peters** approximation



Tommasino & Durante, *Cancers* (2015)

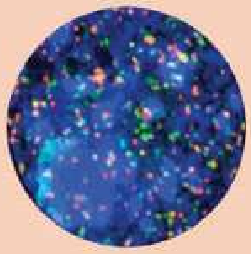
Old Paradigm:
High energy protons and photons are both low LET radiations that have nearly indistinguishable biological effects but different physical characteristics.

➢Protons have dose distribution properties that can be utilized for superior tumor targeting in the clinic.



Photon Proton

➢The DNA damage induced by low LET protons and photons should be essentially equivalent, given their similar track structures at the nm scale.

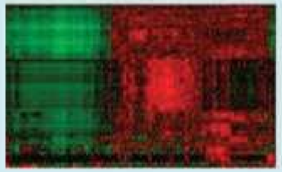


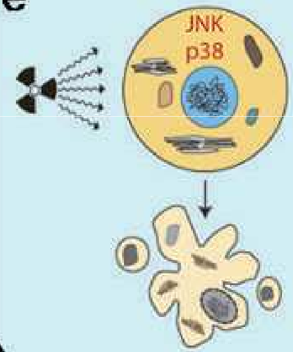
➢The RBE of protons obtained from standard endpoints of cell killing is close to unity (1.1–1.2) and can be applied to more complex endpoints.

New Paradigm:
High energy protons and photons have distinct physical and biological properties.

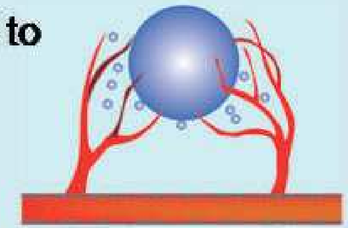
➢Limited applicability of RBE obtained through traditional endpoints that focus on cell death.

➢Protons show unique molecular and cellular responses compared to photon radiation, e.g. induction of more complex DNA damage, differential gene expression, and epigenetic modulation and induction of distinct signaling pathways.





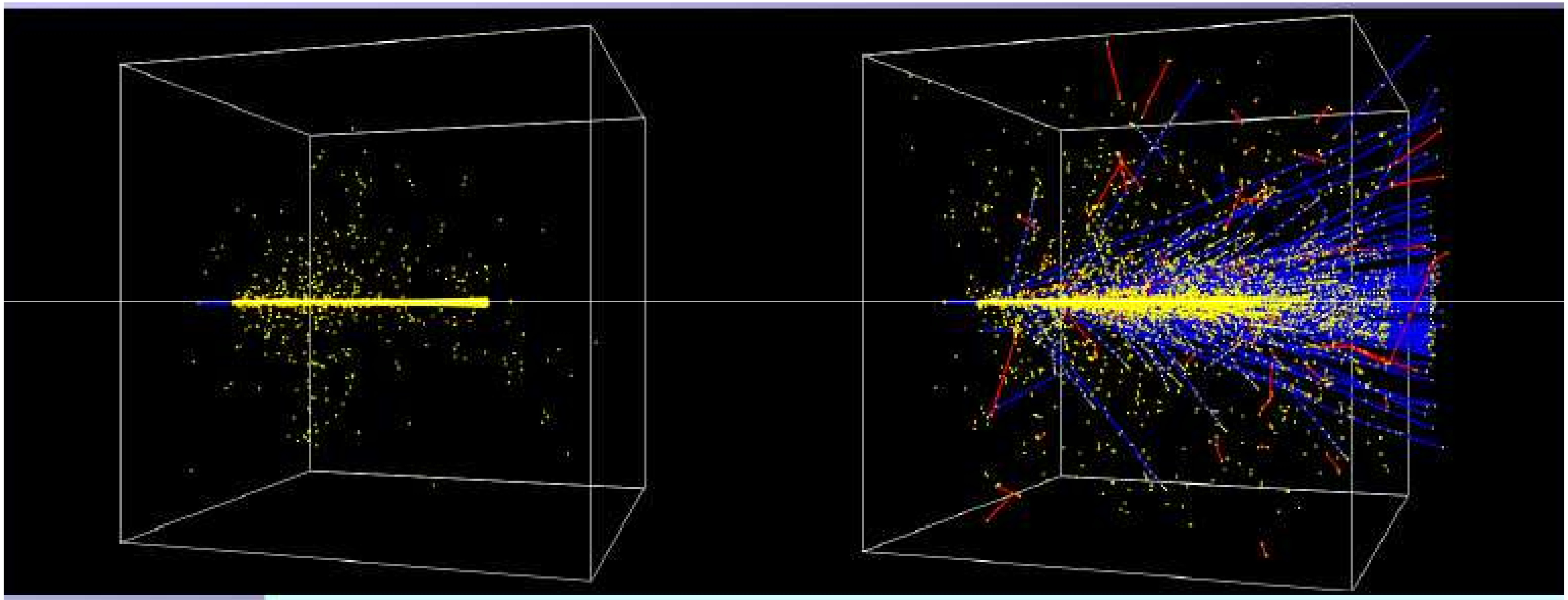
➢Data suggest protons induce complex systems-wide responses that are divergent to those of photons, including inhibition of angiogenesis, invasion and modulation of inflammation.



Girdhani *et al., Radiat. Res*. 2013

2. Projectile fragmentation

C-ions 330 MeV/n in water – simulation by MCHIT



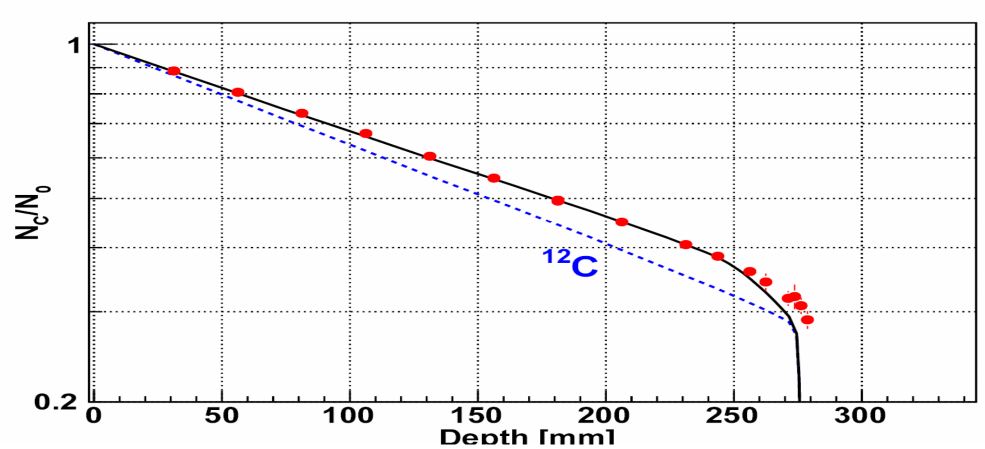
Electromagnetic interactions only

EM interactions + hadronic elastic scattering and fragmentation reactions

courtesy of Igor Mishustin

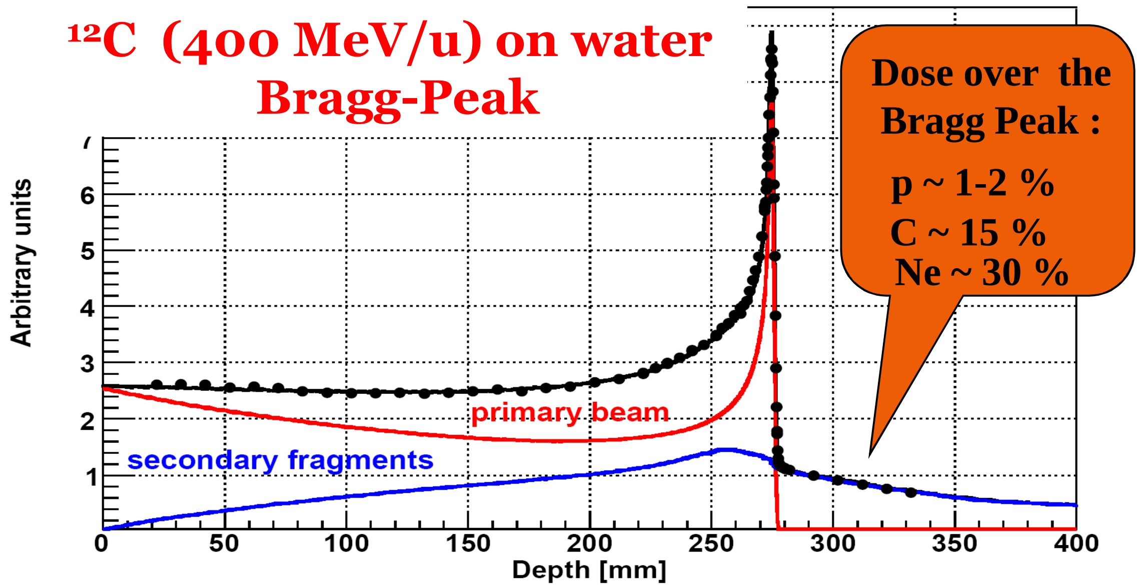
FIAS Frankfurt Institute for Advanced Studies

Projectile fragmentation in heavy-ion therapy



- ✓ Production of fragments with higher range vs primary ions
- ✓ Production of fragment with different direction vs primary ions

- ✓ Mitigation and attenuation of the primary beam:50-70% of the C-ions do not reach the distal edge in typical tretmant
- ✓ Different biological effectiveness of the fragments



Exp. Data (points) from Haettner et al, Rad. Prot. Dos. 2006

Simulation: A. Mairani PhD Thesis, 2007, Nuovo Cimento C, 31, 2008

Fragments detection techniques

Standard techniques exploit the dE/dx measurement (ΔE), calorimetric E measurement, Time of Flight (β) measurement

All this measurement are closely related with the particle identification (PID)

- ΔE vs E -> PID
- ΔE measurement provided PID -> E
- ToF (β) measurement provided PID -> E

Measurements of **target fragmentation** are extremely difficult and highly needed

particle	Ekin/nucl (MeV)	dE/dx (MeV/cm)	Range (cm)
proton	10	42.6	0.1
proton	100	7.4	7.6
He	10	186	0.1
He	100	29	7.6
Be	10	78	0.06
Be	100	114	4.4
Carbon	100	259	2.5
Carbon	400	108	26.3

Data - MC comparison: ^{12}C ions

Build-up of charged fragments for ^{12}C 400MeV/n in water

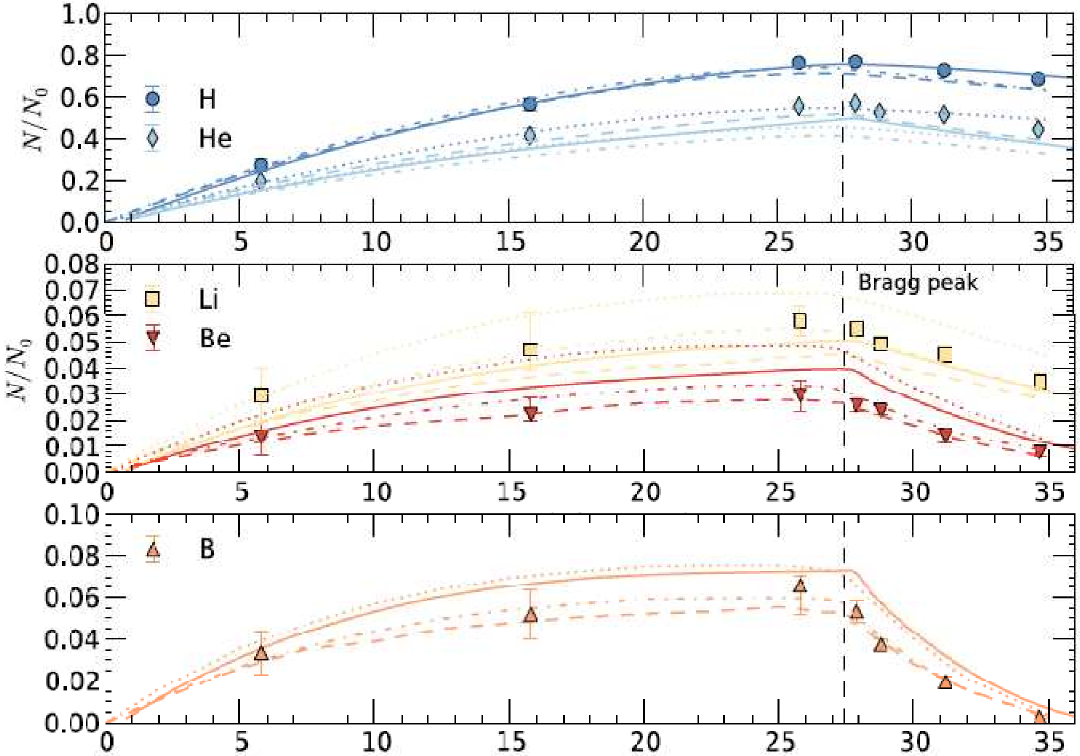
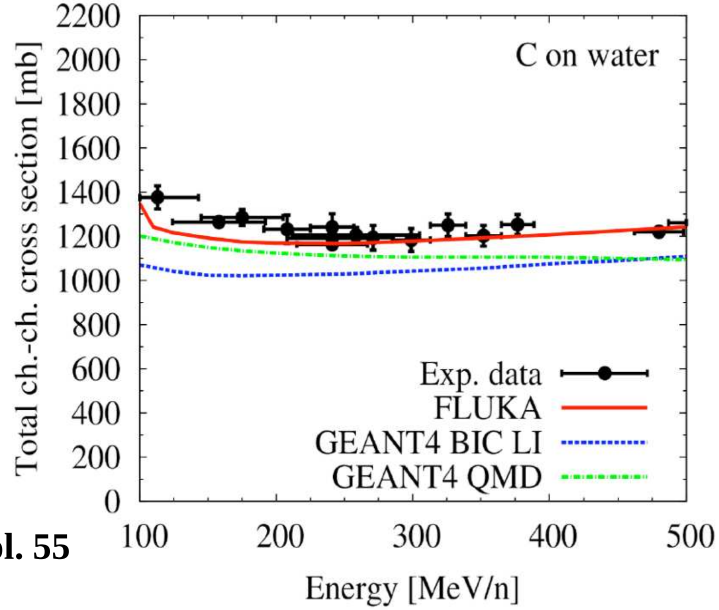


Figure 14. FLUKA, Geant4–QMD, Geant4–BIC LI (Böhlen *et al* 2010) and SHIELD-HIT10A simulations of the relative yield of fragments emitted within a 10° forward angle from a 400 MeV/u ^{12}C beam in water, compared with experimental data (Haettner *et al* 2006). Dashed line: FLUKA simulation. Dashed-dotted line: Geant4–QMD simulation. Dotted line: Geant4–BIC simulation. Solid line: SHIELD-HIT10A simulation. The markers are experimental data. Where error bars are not visible, they are smaller than the markers.

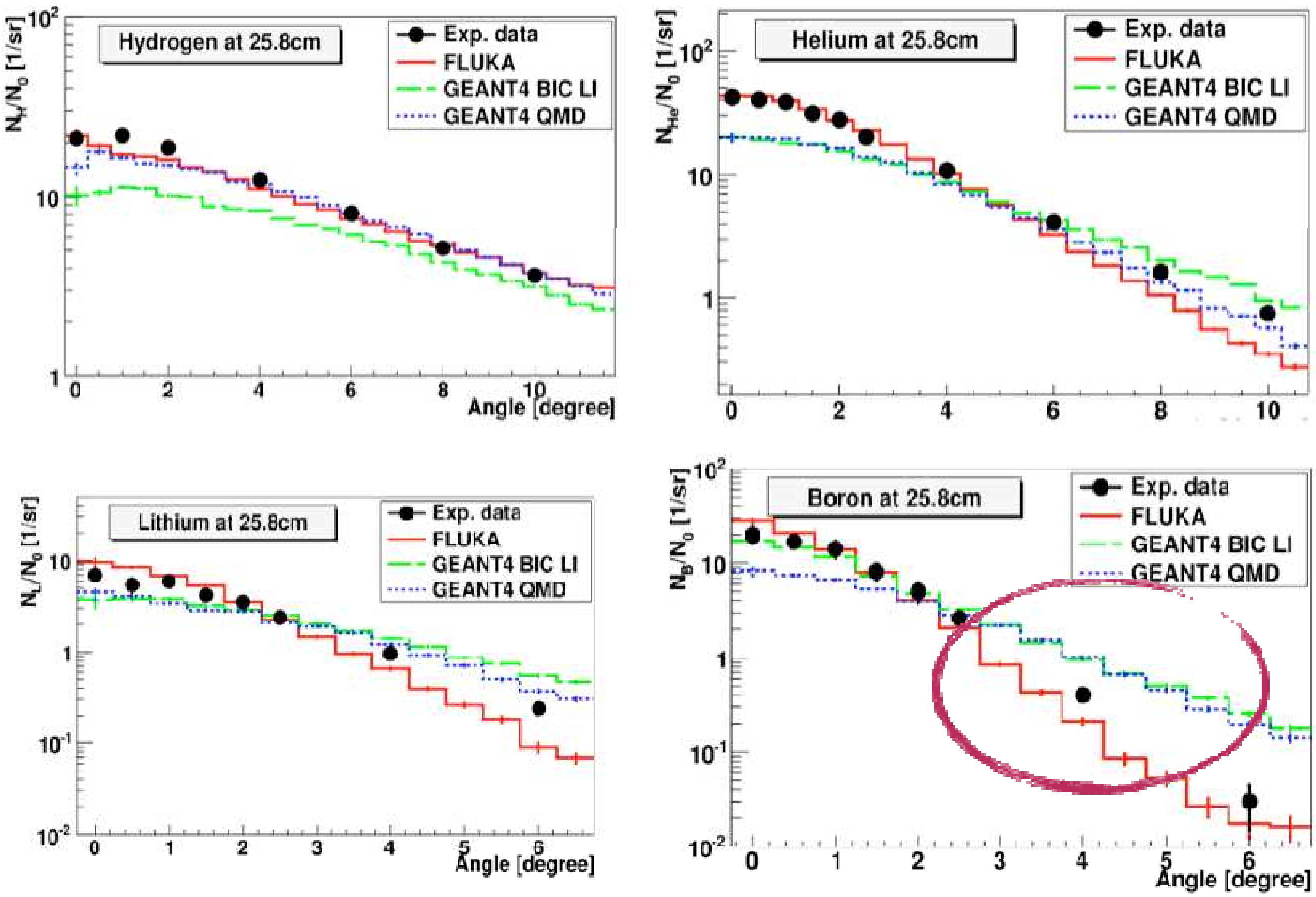
Integral quantities (fragment yields, charge changing cross sections) are generally within 10-20%



Bolhen et al, Phys. Med. Biol. 55 (2010) 5833–5847

Data - MC comparison: ^{12}C ions

Differential/double- differential quantities (vs angle and/or energy) ➔ larger discrepancies found



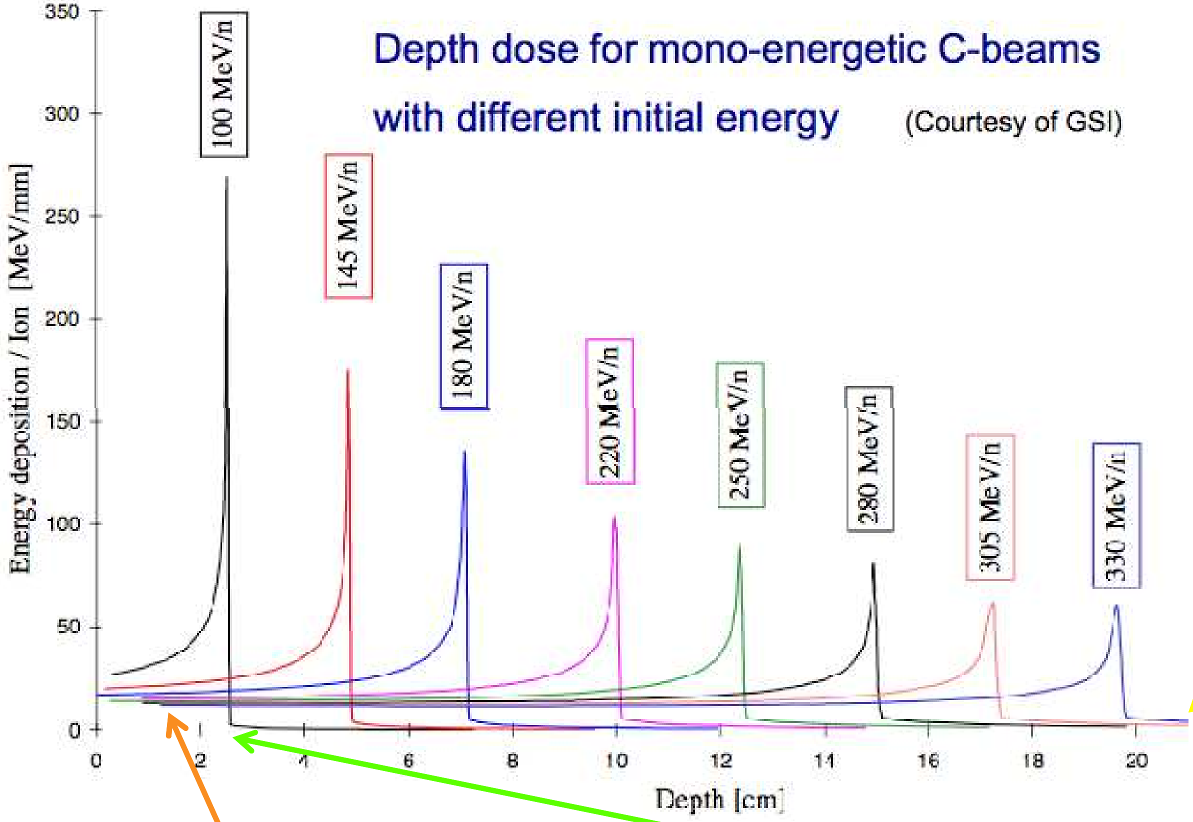
Bolhen et al, Phys. Med. Biol. 55 (2010) 5833–5847

NB: the accuracy on delivered dose MUST be of the order of few %

Some MC benchmarks:

Sommerer et al. 2006, PMB
Garzelli et al. 2006, ArXiv
Pshenichnov et al. 2005, 2009
Mairani et al. 2010, PMB
Böhlen et al. 2010, PMB
Hansen et al. 2012, PMB

Recent thin target, Double Diff Cross Section C-X measurements



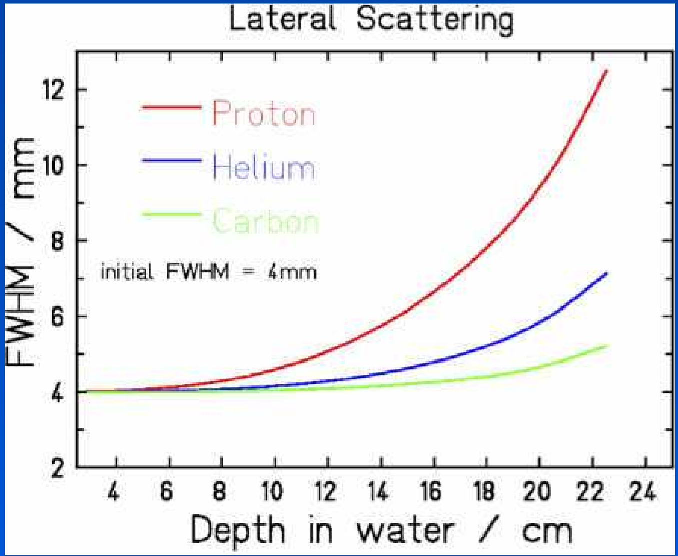
The community is exploring the interesting region for therapeutical application.

GSI 400 AMev C beam
FIRST experiment

GANIL 95AMev C beam - E600 collaboration (2011)

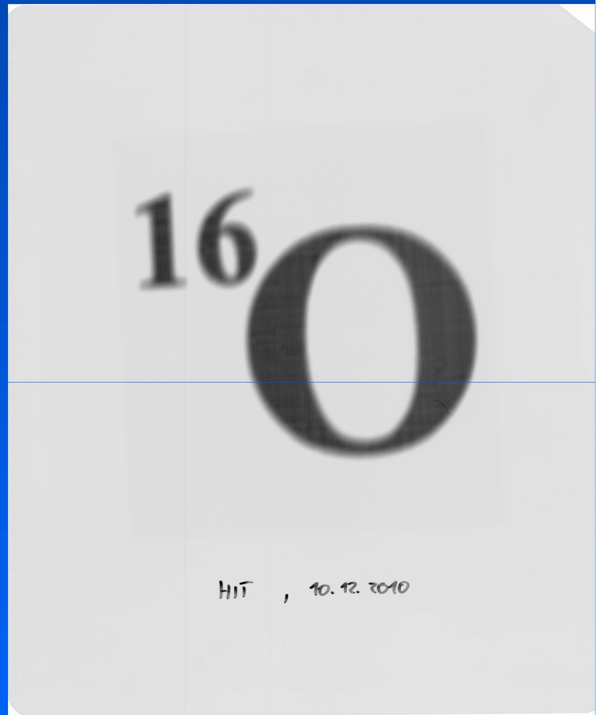
LNS 62 AMev C beam
FRAG experiment

3. Fragmentation of other ions

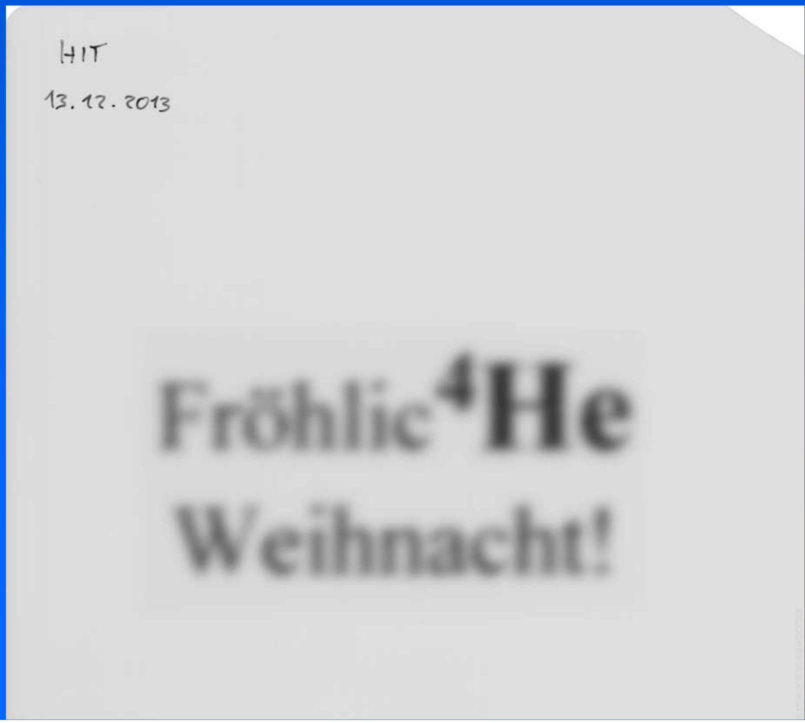


Penumbra comparison (90% => 10%):

Protons:	**17,4 mm**
Helium4:	**10,9 mm**
Carbon:	**7,4 mm**



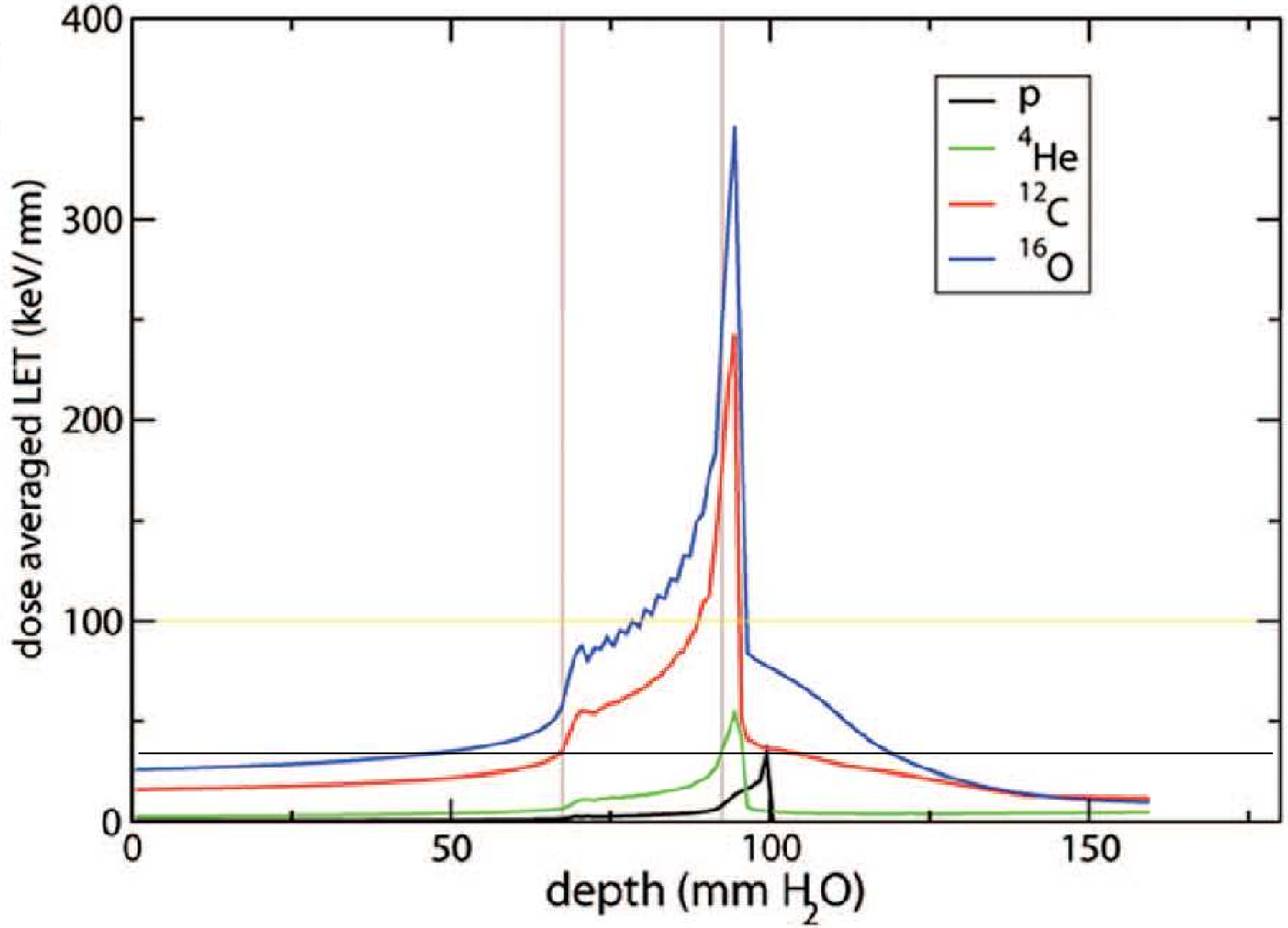
Rasterscan @ HIT-R+D-Cave



Courtesy of Thomas Haberer, HIT

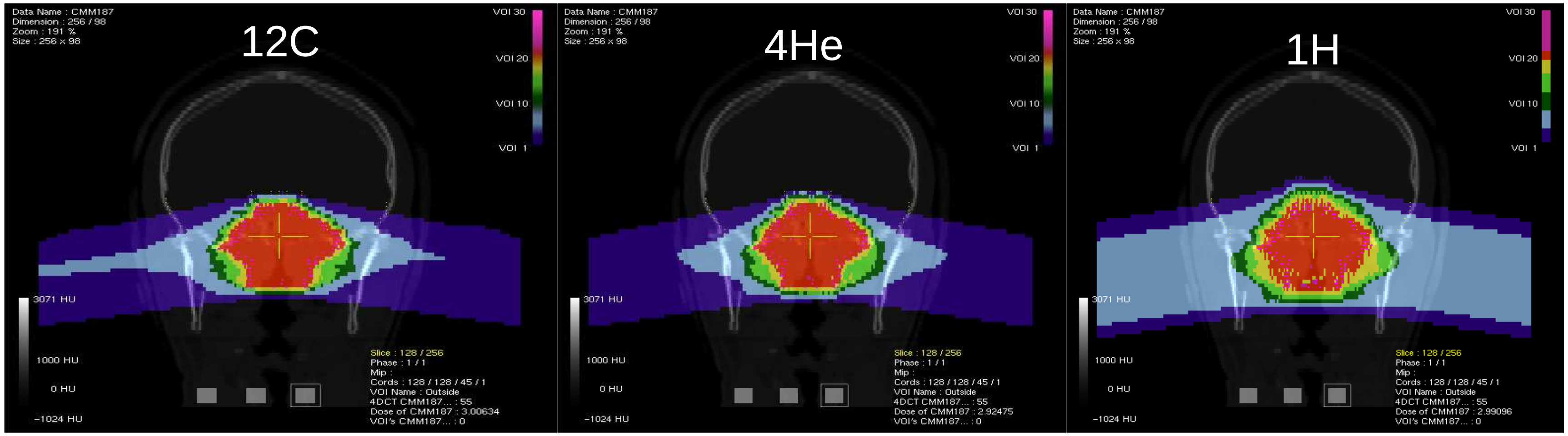
Trento Institute for
Fundamental Physics
and Applications

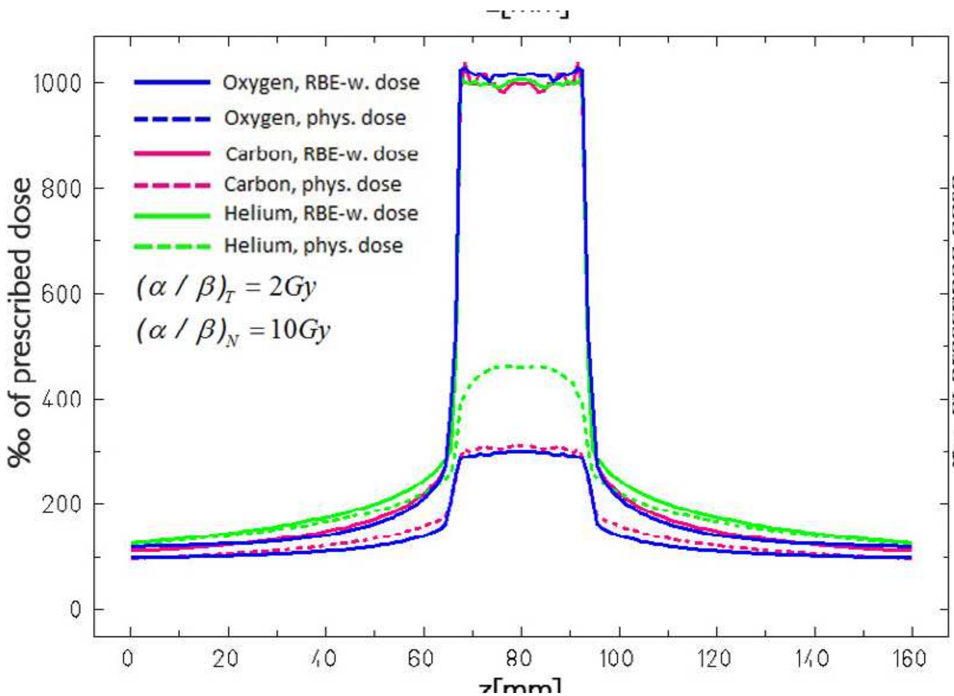
Why carbon?

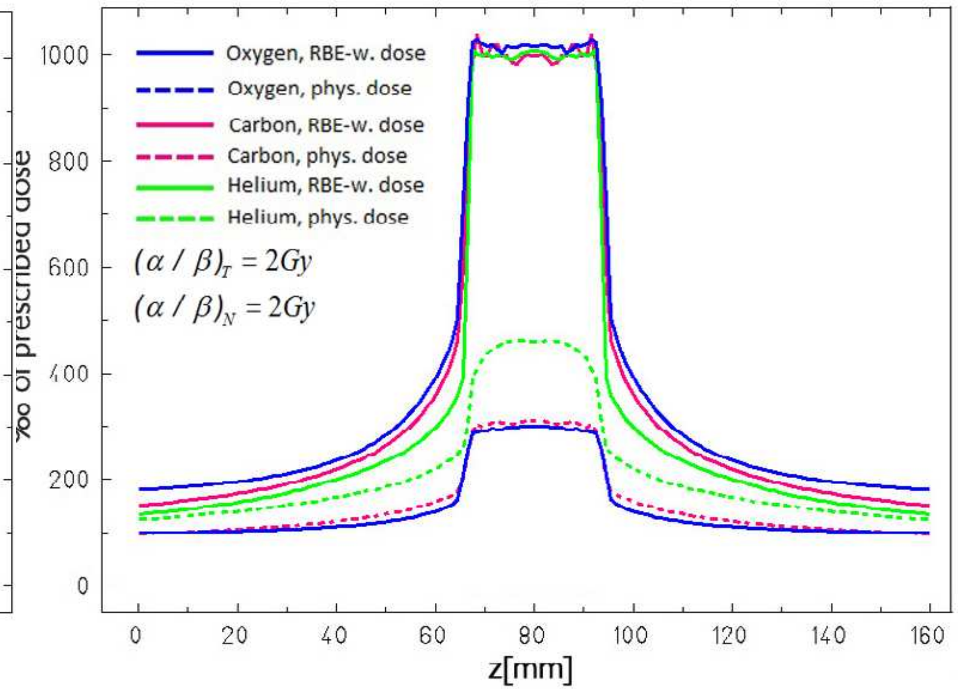


Simulations of different ions for particle therapy

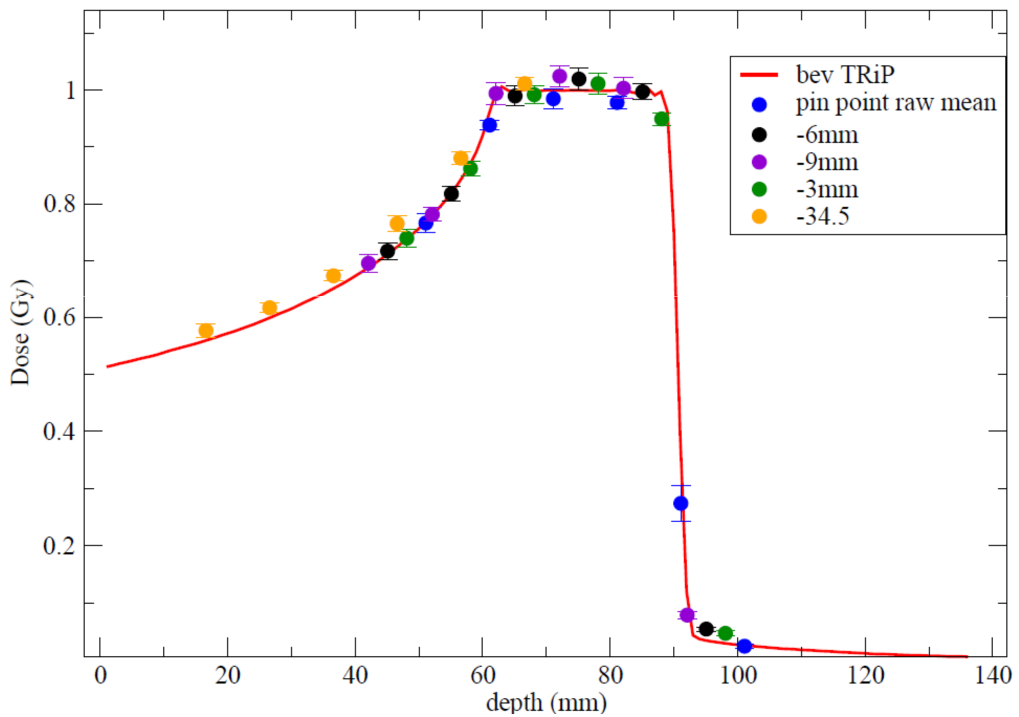
Grün et al., Med. Phys. 2015; Scifoni et al., EPJD 2014

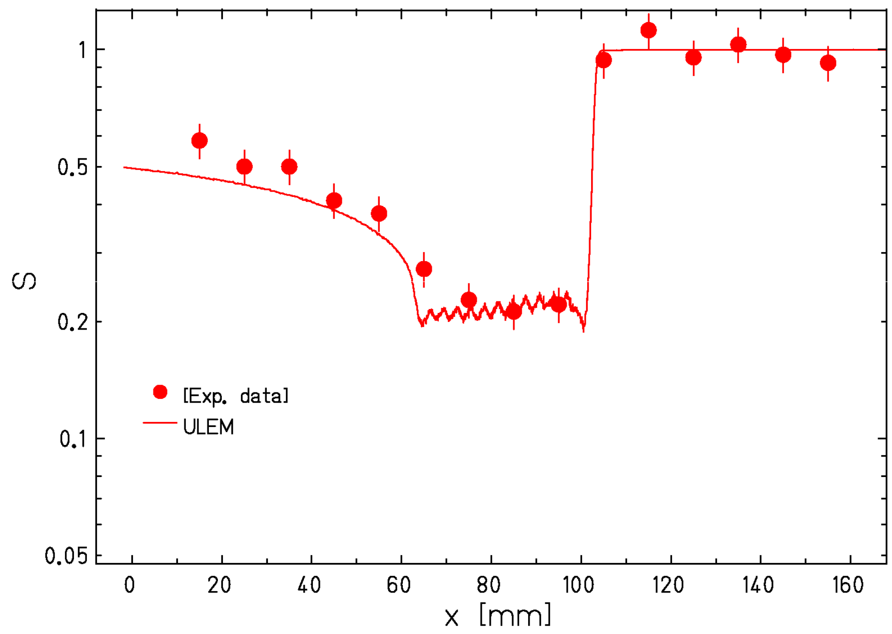






Helium: pre-clinical experimental studies



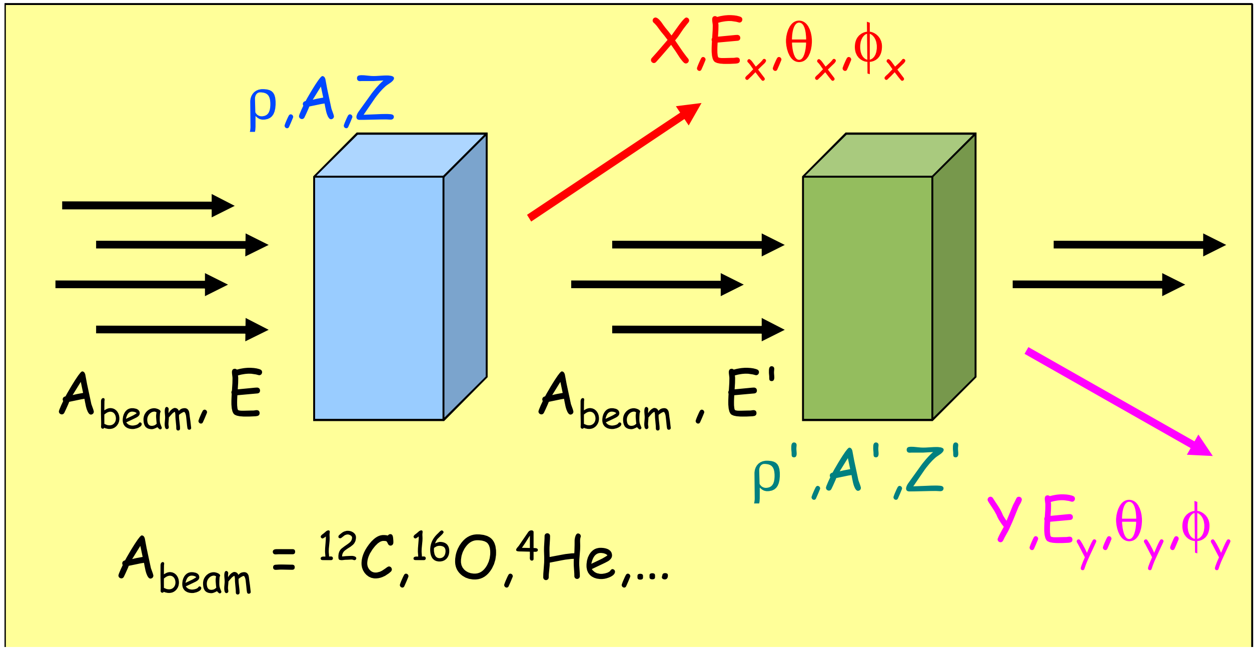


SOBP, He-ions
Krämer *et al.*, Phys. Med. Biol. 2016

What we still miss to know about light ions fragmentation in 2018?

Data exist at 0^0 or on thick target. But we need to know, for any beam of interest and on thin target:

- Production yields of Z=0,1,2,3,4,5 fragments
- d^2□/d□dE wrt angle and energy, with large angular acceptance
- For any beam energy of interest (100-500 AMeV)
- Thin target measurement of all materials crossed by beam



- Not possible a complete database of measurements
- We need to train a nuclear interaction model with the measurements

4. Range uncertainties

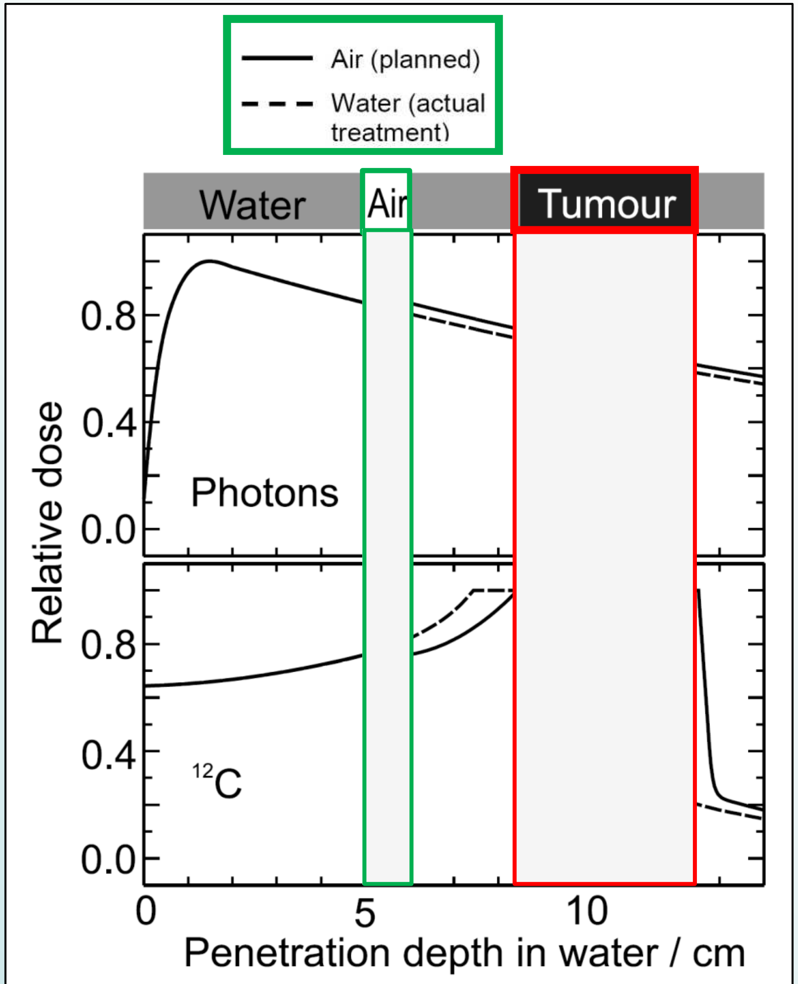
TPS dose calculation errors

- Inhomogeneities, metallic implants
- Conversion HU in ion range
- CT artifacts

Difference TP / delivery

- Daily setup variations
- Internal organ motion
- Anatomical / physiological changes

Daily practice of compromising dose conformality for safe delivery



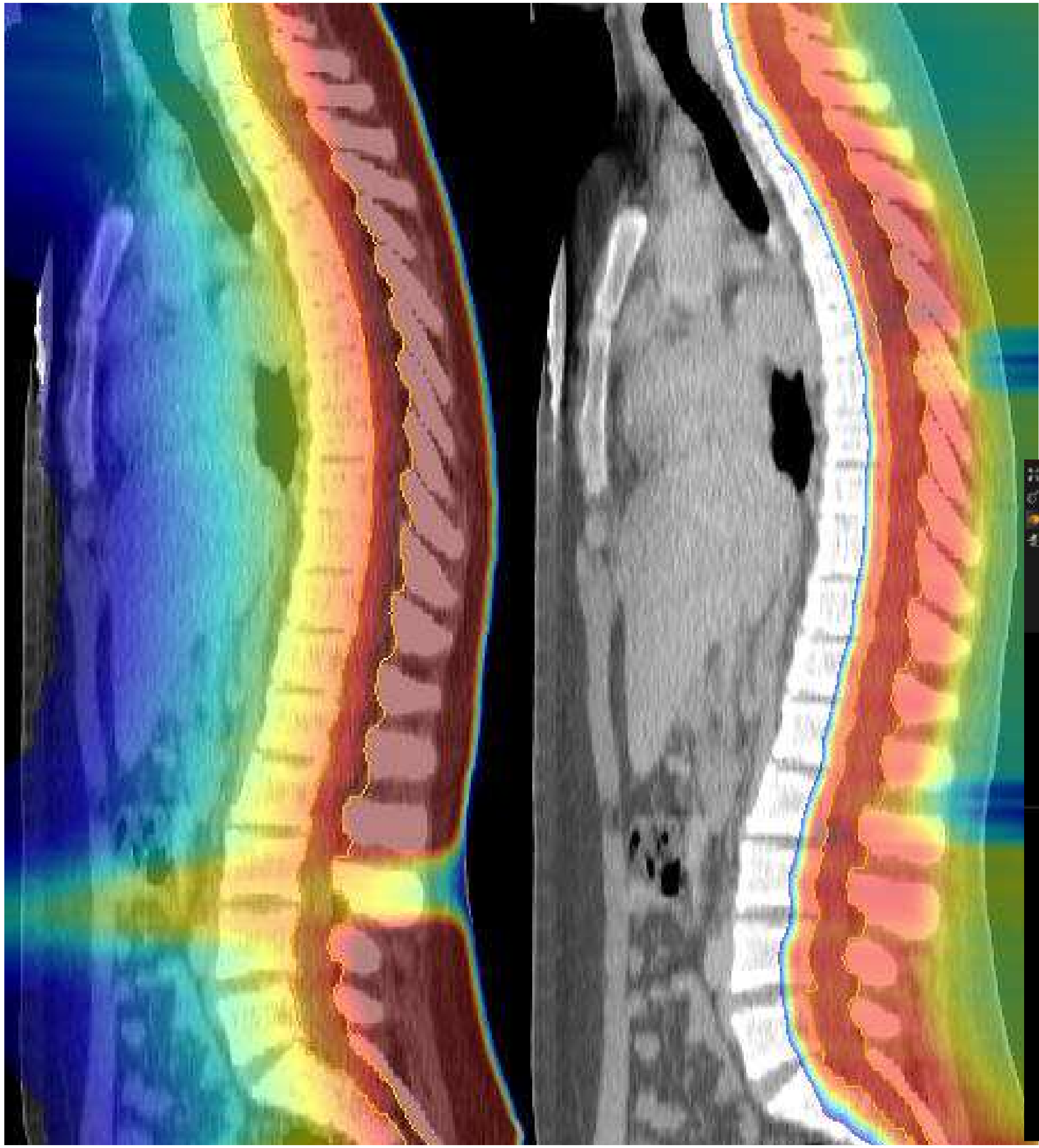
After Enghardt 2005

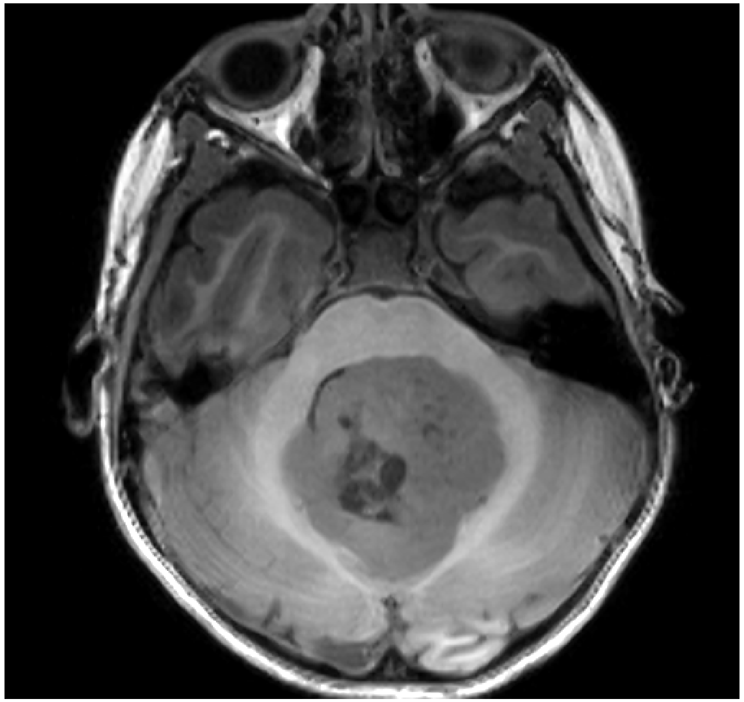
Courtesy of Wolfgang Enghardt

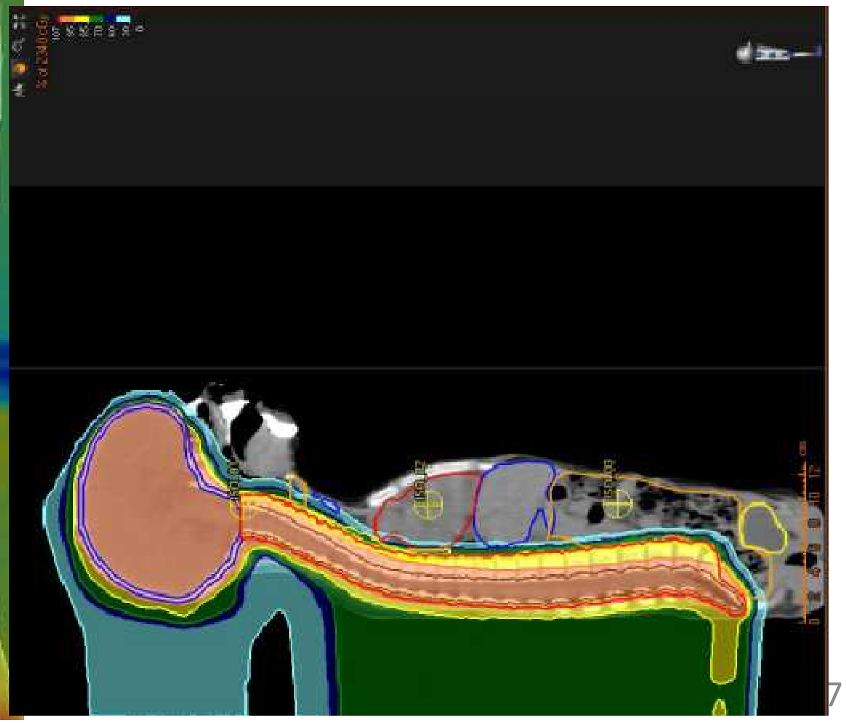
Tumori pediatrici

•Pianificazione In trattamento Ultimo giorno 6 m post-P

PEDIATRIC MEDULLOBLASTOMA

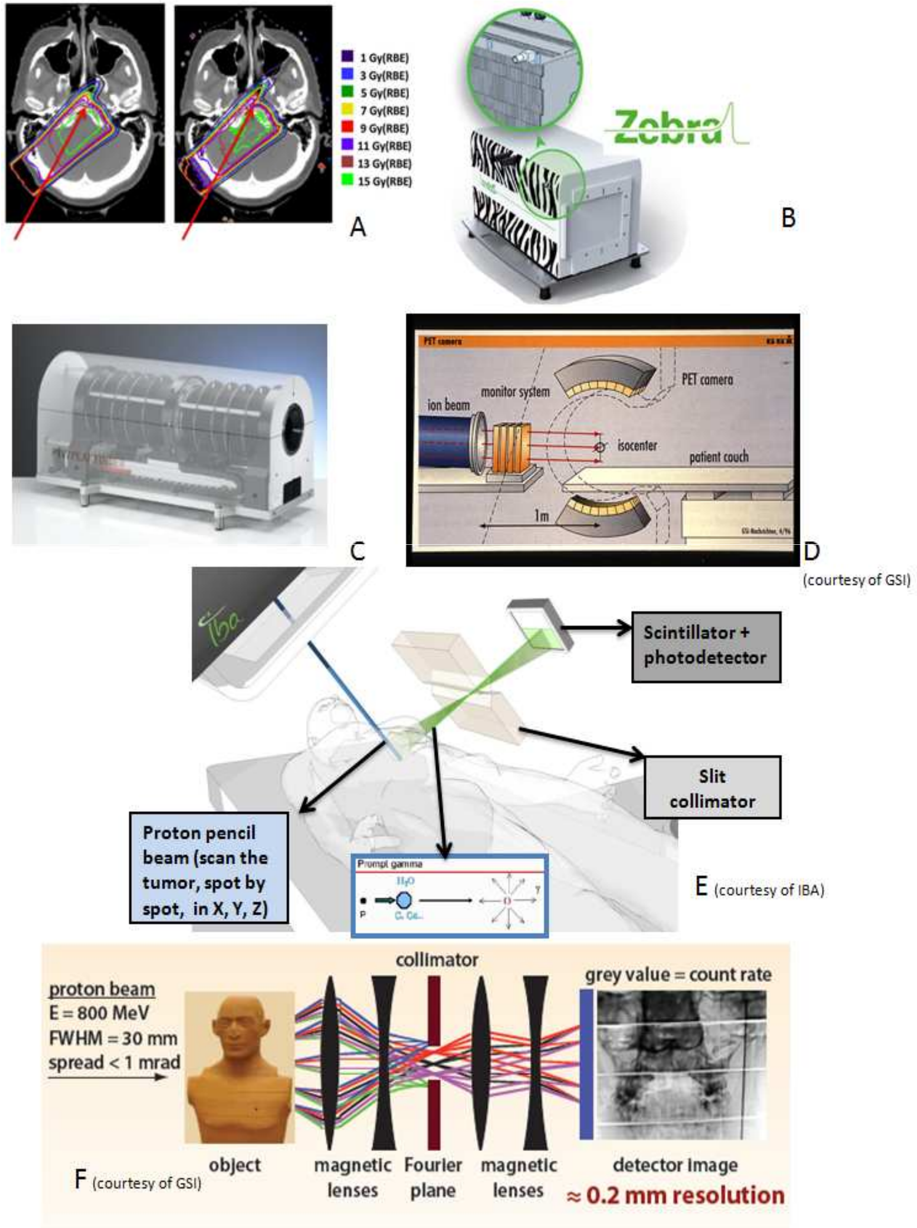






Range verification

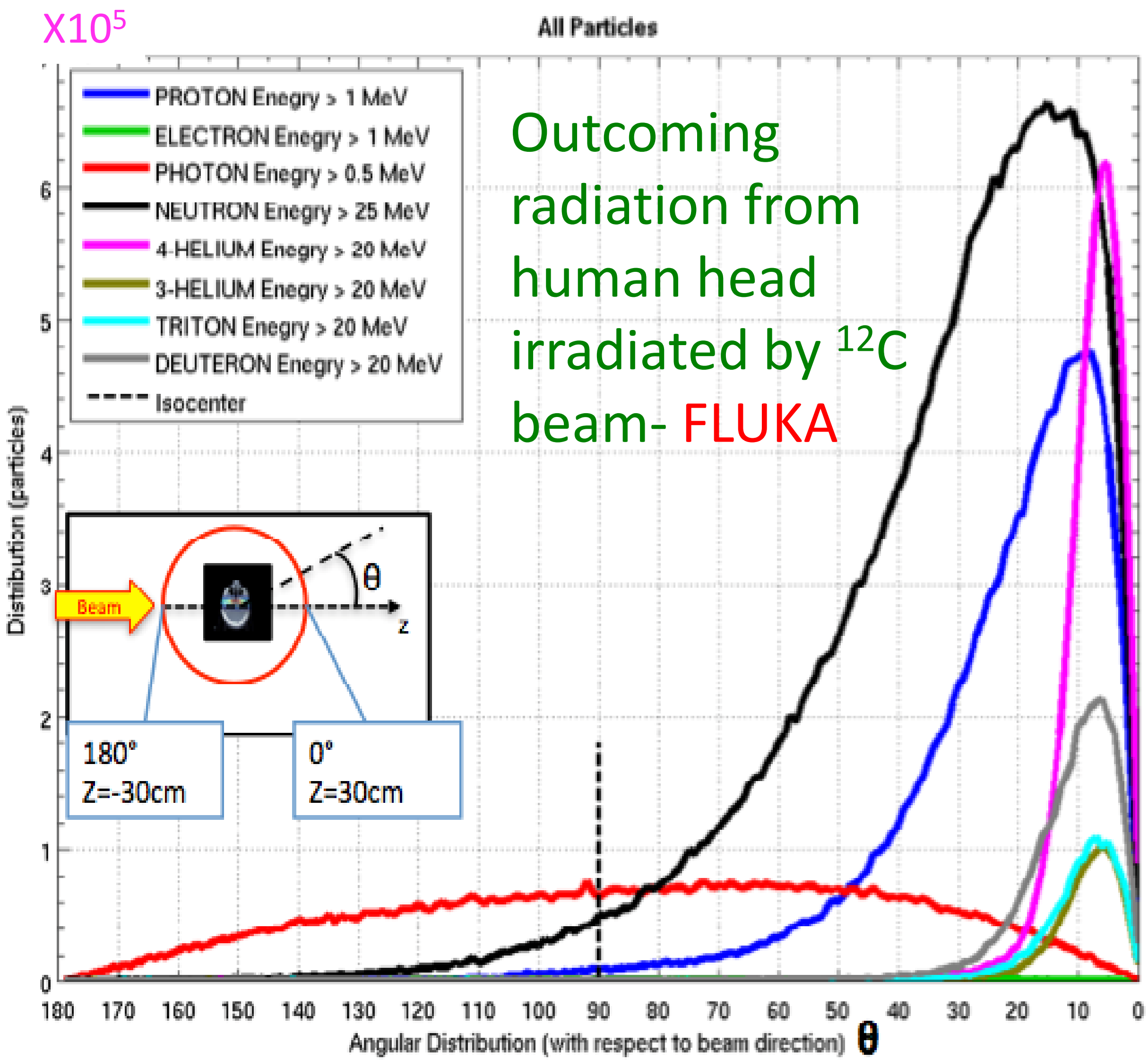
Source of range uncertainty in the patient	Range uncertainty
Independent of dose calculation:	
Measurement uncertainty in water for commissioning	±0.3 mm
Compensator design	±0.2 mm
Beam reproducibility	±0.2 mm
Patient setup	±0.7 mm
Dose calculation:	
Biology (always positive)	+0.8 %
CT imaging and calibration	±0.5 %
CT conversion to tissue (excluding I-values)	±0.5 %
CT grid size	±0.3 %
Mean excitation energies (I-values) in tissue	±1.5 %
Range degradation; complex inhomogeneities	- 0.7 %
Range degradation; local lateral inhomogeneities *	±2.5 %
Total (excluding *)	**2.7% + 1.2 mm**
Total	**4.6% + 1.2 mm**



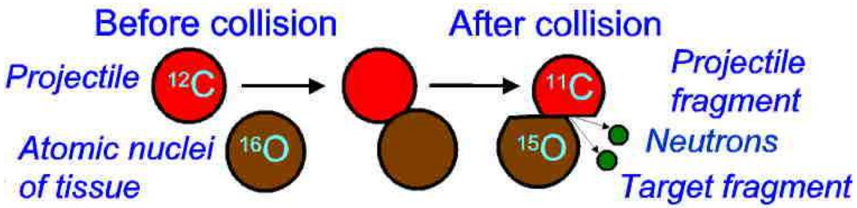
Fragmentation and beam monitoring

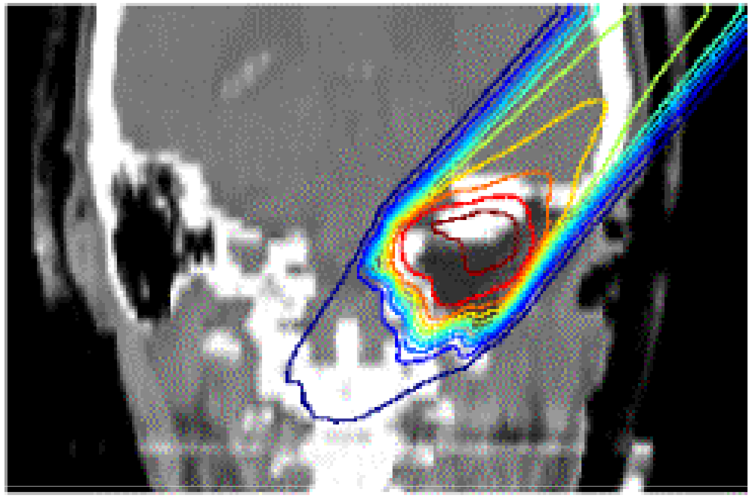
The p, ^{12}C beams generate a large amount of secondaries.

Prompt single gamma, positrons, protons and neutrons can be used to track the beam inside the patient

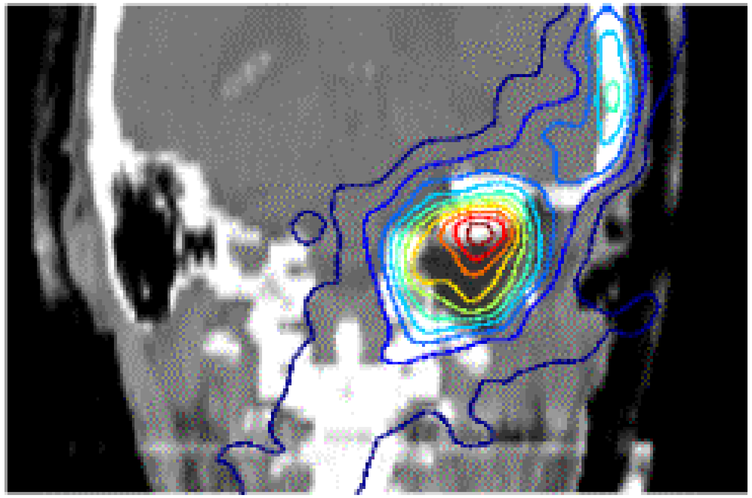


In situ control with PET

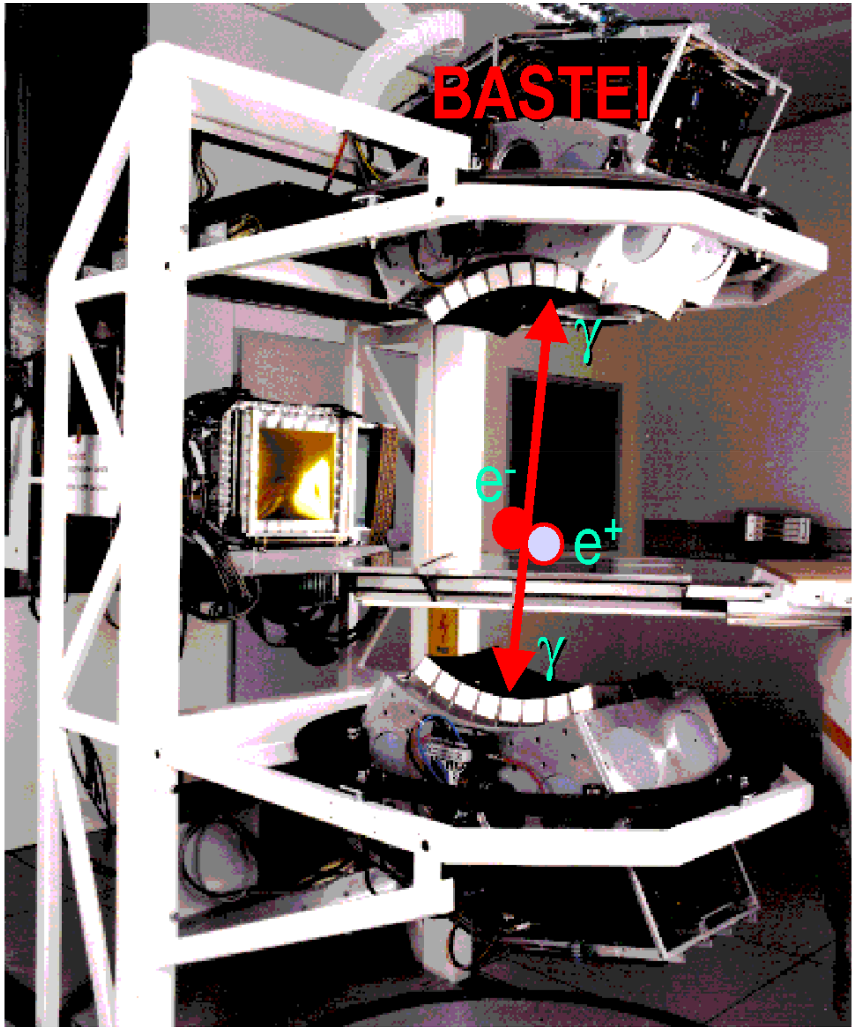




dose plan

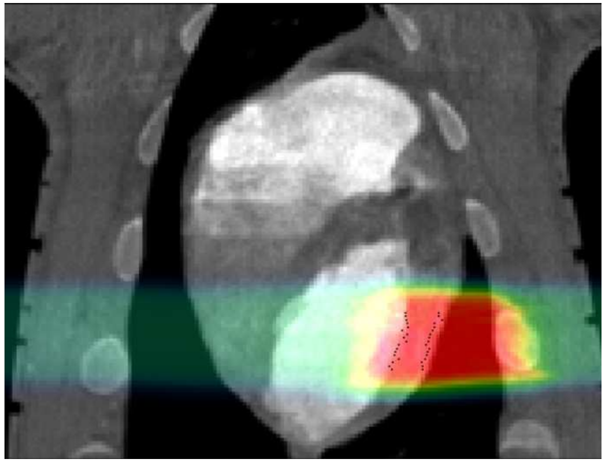


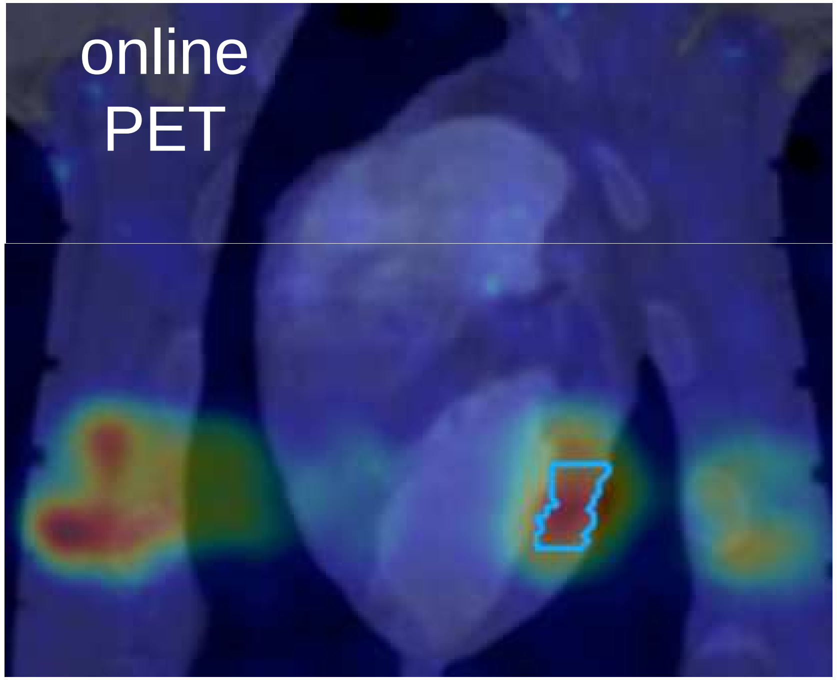
measured

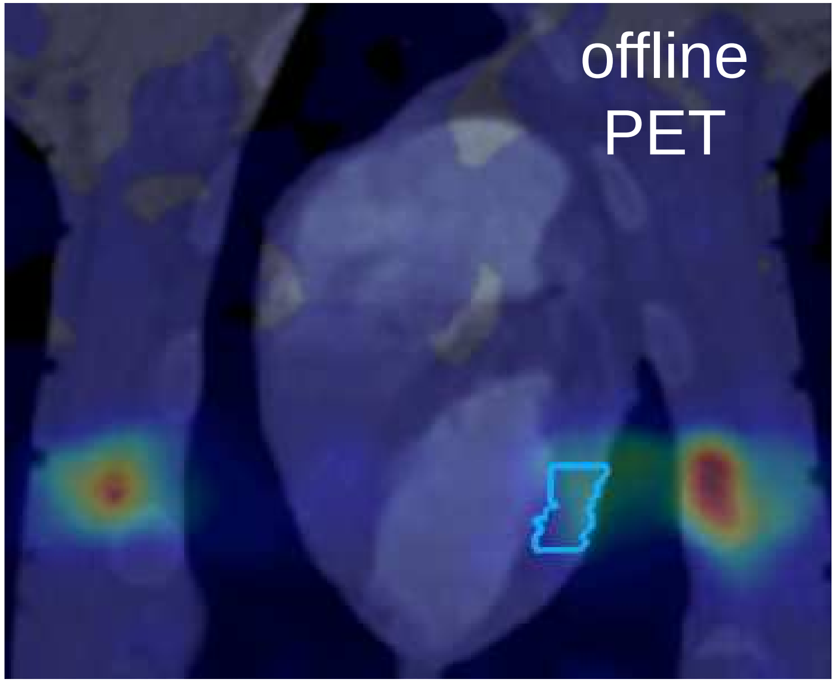


Courtesy of Wolfgang Enghardt, HZDR, Dresden

Treatment plan – TRiP984D







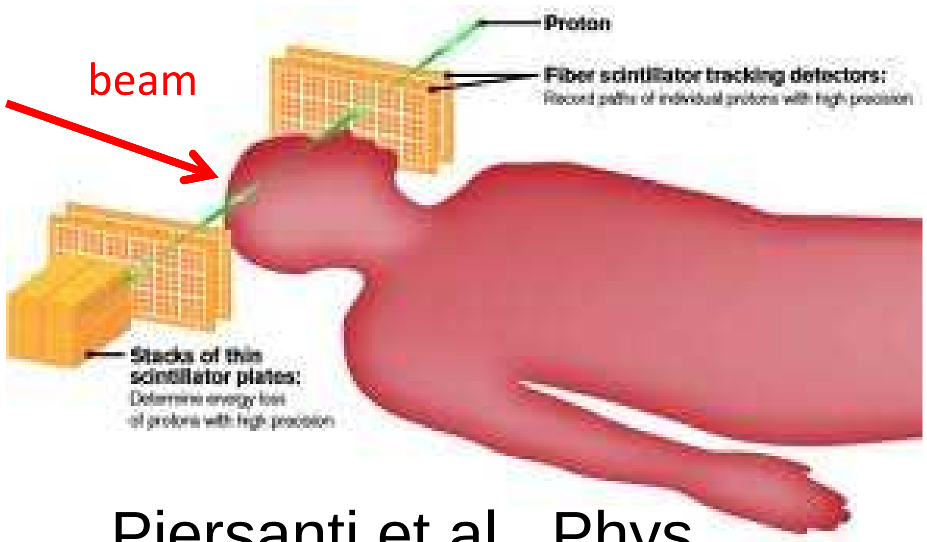
Monitoring secondary charged particles

Charged particles have several nice features as

- The detection efficiency is almost one
- Can be easily back-tracked to the emission point-> can be correlated to the beam profile & BP

BUT…

- They are not so many
- Energy threshold to escape ~ 100 MeV
- They suffer multiple scattering inside the patient -> worsen the back-pointing resolution



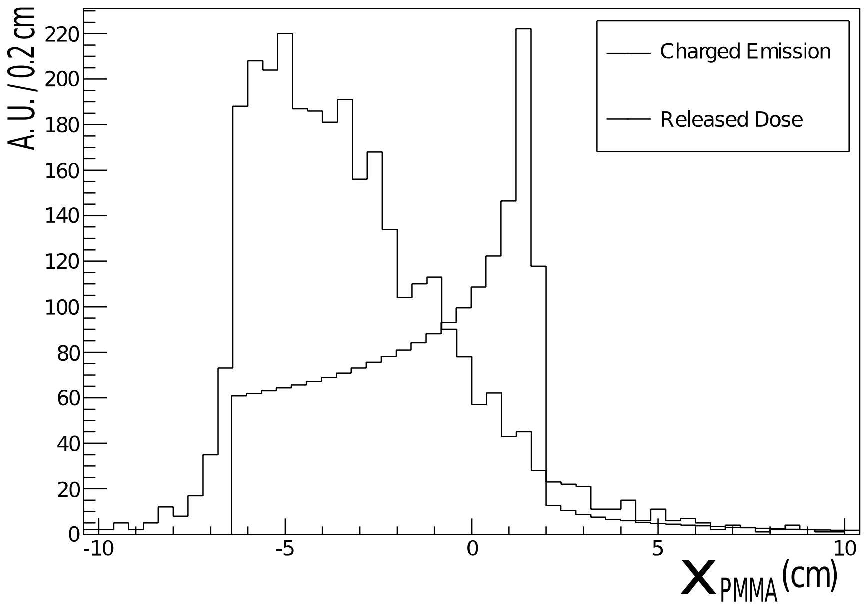
Piersanti et al., Phys. Med. Biol. 2014

Secondary protons & beam monitoring

There are indications that emission point distribution of 100-150 MeV secondary protons provides info on the BP position

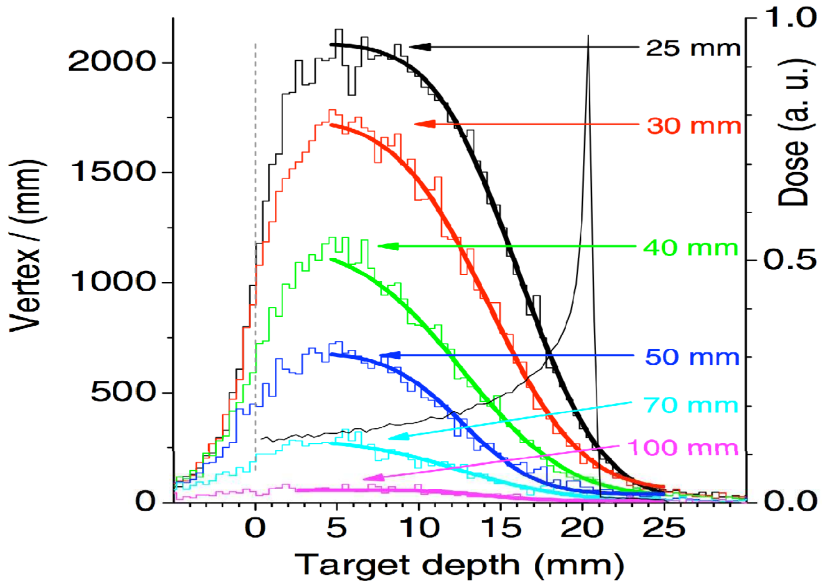
Measured emission distribution shape of protons as detected outside a 5 cm thick PMMA at 90^0 wrt the direction of 220 AMeV ^{12}C beam

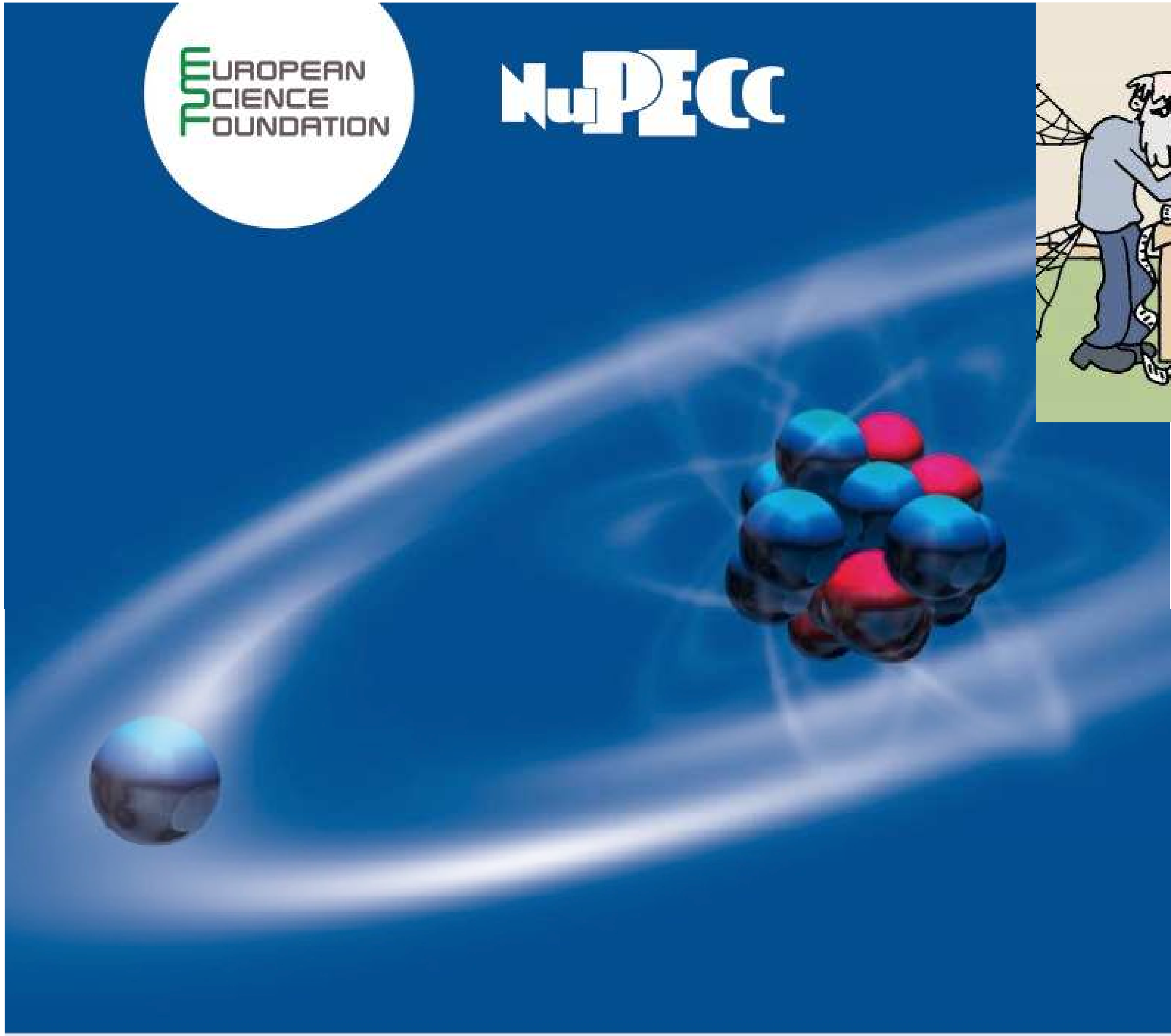
L. Piersanti et al Phys. Med. Biol 2014



Simulated emission distribution shape of protons as detected ouside different PMMA thickness at 30^0 wrt the direction of 95 AMeV ^{12}C beam

E. Testa et al Phys. Med. Biol. 57 4655





Nuclear Physics European Collaboration Committee (NuPECC)

Nuclear Physics for Medicine

www.nupecc.org

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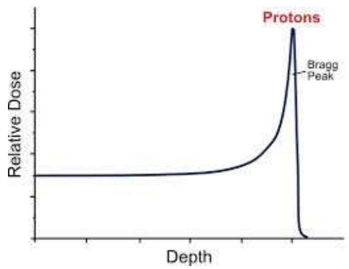
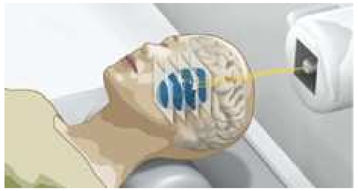
April 2014 – Print run: 2000

Finishing the job: how many things we could do with more nuclear physics….

- Ultrafast treatments (seconds)
- Moving targets (lung, abdomen….)
- Radiosurgery (single fractions for cancer and noncancer diseases)
- Oligometastasis (3-7 treated simultaneously)
- Image-guided adaptive treatments (hypoxia, cancer stem cells…..)



Bragg peak as the XXI century scapel



Summary

Eventually, the cost effectiveness of particle therapy will be decided by clinical trials but nuclear physics should bring the methodology from „experimental“ to „routine“

Nuclear fragmentation measurements are highly needed for treatment planning, use of new ions, calculations of the biological effectiveness, and online monitoring of beam delivery

- Double-differential cross-sections are particularly important for Monte Carlo codes, now entering (via GPU) in commercial TPS
- Target fragmentation studies are technically challenging but are essential for protontherapy and for future He-ion therapy